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(Continued)

THE SIGNIFICANCE OF "VALENCE" IN ANTIBODY INTERACTIONS* † ‡

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A LANDMARK in the history of immunology was the development of the so-called "Unitarian" hypothesis, which, according to one formulation,[1] is the belief that: "... were we working with a single antigen, in a pure state, one variety of antibody only would be produced. ... As a result of the union (with antibody) the antigen is altered in its physical and in its chemical behavior. The resultant reaction which may be observed with this sensitized antigen (agglutination, precipitation, complement fixation, sensitizing effects in the anaphylactic sense, etc.) is determined not by differences in the nature of the antibodies with which the antigen has united, but rather by the physical state of the antigen itself, the nature of the co-operative substances (alexin, leucocytes, tissue cells), and by the environmental conditions under which the observations are made." Within the past fifteen years, however, it has become apparent that this hypothesis requires modification since (1) it does not recognize the possibility of observable differences among antibodies produced against a single antigen, and consequently (2) it does not take cognizance of the fact that variations in antibody may influence the behavior of the antigen-antibody complex.

In a classic experiment Landsteiner and van der Scheer[2] demonstrated that the antiserum developed by injecting rabbits with *p*-aminosuberanilic acid coupled to horse serum contained a mixture of antibodies with differing reactivities

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*The term "valence" is used here to denote the number of specific binding sites on a particular molecule either antigen, hapten, or antibody. This usage differs from what is customarily intended in the chemical literature. It also differs from what is involved in the older immunological usage, where the term "valence" refers to the number of different antigens with which a single antiserum can react.

†The antibodies referred to in this note are those which occur in serum.

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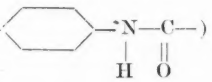
toward the following related groupings coupled to casein:

B—$(CH_2)_6$ COOH *p*-aminosuberanilic acid
B—$(CH_2)_5$ COOH *p*-aminopimelanilic acid
B—$(CH_2)_4$ COOH *p*-aminoadipanilic acid
B—$(CH_2)_3$ COOH *p*-aminoglutaranilic acid

(B is H_2N—  —N—C—)
H O

In a detailed, quantitative extension of this work Pauling, Pressman, and their collaborators[3] provided clear-cut evidence that antisera for other haptens also were composed of antibodies of various reactivities. These authors further demonstrated that, under certain conditions, the heterogeneity of their antibody solutions (i.e., antisera) could be described in mathematical form.[4]

Since the antibodies for a single antigenic grouping are a heterogenous mixture of molecules of differing reactivities, it is not surprising that the antiserum for a protein would exhibit as much heterogeneity, or even more—since a protein antigen can be regarded as an assembly of many antigenic determinants. In fact, Heidelberger and his associates[5, 6] and Pappenheimer[7] have found in rabbit and in horse antisera to egg-albumin (Ea) such great diversity of antibody-reactivity that while most of the antibodies could form insoluble, or precipitating, complexes with Ea, there were others which could only form soluble, or nonprecipitating, complexes with Ea. Furthermore, Miller and Campbell[8] found that the serum of an egg white-sensitive patient contained antibody that could only form soluble, nonprecipitating complexes with egg albumin. Thus, the properties of the antibody must be taken into account in order to describe adequately the behavior of the antigen-antibody complex.

This distinction between precipitating and nonprecipitating antibodies may be highly significant in allergy, since in human hypersensitive states the antigen-antibody complexes are almost always soluble, whereas in many immune states the complexes form precipitates. It is for this reason, among others, that insight into the mechanism of the precipitative (and agglutinative) reaction is of considerable importance. One explanation of this phenomenon which has been strongly supported in the past decade is known variously as the "lattice" or "framework" theory.[9, 10, 11] According to this hypothesis when antigen and antibody are mixed, each antigen molecule can combine with several antibody molecules, and each of the latter, in turn, can combine with other antigen molecules, the process continuing on to form larger and larger aggregates which finally settle out of solution.

This viewpoint, which has great simplicity, requires that two assumptions be true: first, that an antigen molecule can combine with more than one antibody molecule, and, second, that an antibody molecule be capable of combining with more than one antigen molecule (i.e., an antibody "valence" of two or more). The first postulate, namely, that antigen molecules have more than one binding site for antibody, can scarcely be doubted. Thus, if one adds increasing amounts of bovine serum albumin* to rabbit anti-BSa serum, one obtains a

*Hereafter referred to as BSa.

precipitin curve like that of Fig. 1.[12] The precipitates that form in the zone of relative antibody excess have mole-ratios of antibody to antigen of the order of 5 or 4 or 3 to 1, i.e., 1 BSa molecule in these precipitates has combined, on the average, with 5 or 4 or 3 antibody molecules.

The second assumption required by the lattice theory, namely, that antibody is multivalent with respect to antigen, has been more difficult to establish unequivocally. In the case of protein-antiprotein and polysaccharide-antipolysaccharide systems, the results obtained from studies of the mole-ratios of antibody to antigen in the specific precipitates formed in the presence of antigen excess

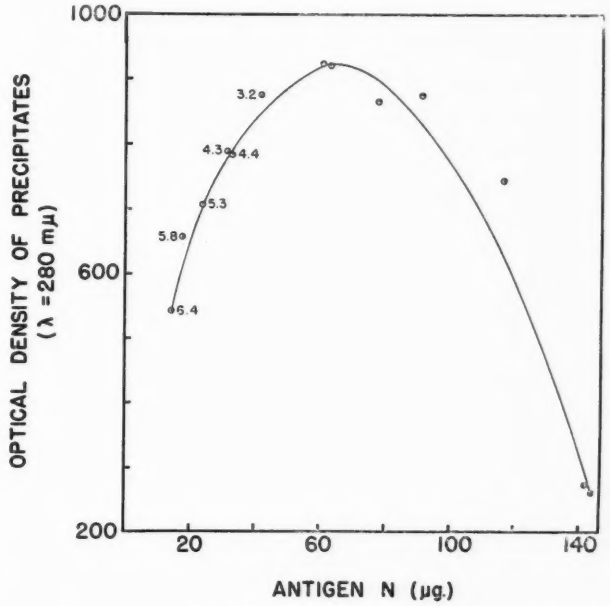


Fig. 1.—A precipitin curve with BSa and anti-BSa serum, adapted from ref.[12] The numbers on the curve represent the approximate molecular ratio of antibody to BSa in the corresponding precipitates.

have not served to establish the number of binding sites on the antibody.[13] However, in experiments which made use of synthetic polyhaptenic dyes as specific precipitating agents Pauling, Pressman, and Ikeda[14] found antibody—"antigen" mole-ratios in the precipitates of about one (actually 0.8); on the basis of this finding, these authors conclude that one antibody molecule, on the average, can combine with approximately 2 "antigen" (polyhapten) molecules.* Furthermore, Pappenheimer et al,[16] using the ultracentrifuge to study the composition of soluble diphtheria-toxin-antitoxin complexes formed in the presence of a great excess of toxin, found that one antitoxin molecule can combine with more than one, and at most with two, molecules of toxin. These results indicate that the

*Boyd and Behnke[15] have attempted to study the aggregation of polyhaptenic dyes and, on the basis of their results, have suggested that the validity of this conclusion is rendered doubtful by the possibility of polymerization of the "antigen" (polyhaptenic dye). Although the results of Boyd and Behnke are suggestive they are by no means adequate to establish the significance of their objection.

antibody (antitoxin) molecule has more than one binding site; however, since the effective number of binding sites of the antigen (toxin) molecule is not known in these complexes, the results do not measure the actual number of binding sites of the antibody.

We have recently approached the problem of determining the number of specific binding sites on an antibody molecule through the use of a procedure known as equilibrium dialysis.[17] In these experiments we have immunized rabbits with sheep serum to which had been coupled the haptenic grouping *p*-azophenylarsonic acid.* In order to extract from the rabbit antisera those antibodies with a specific orientation for R, the following procedure was carried out[2]: The rabbit antisera were mixed with human red-blood-cell stromata to which R had been coupled. After a suitable incubationary period the stromata, to which anti-R antibodies were now specifically bound, were collected by centrifugation; these were then washed with saline to remove nonspecific protein, resuspended in saline, and the antibody separated from the stromata by adjustment of the pH to about 3.5.† In the solutions of purified antibody which were thus prepared at least 90 per cent of the protein could be precipitated by R-stromata, and, furthermore, these solutions could form precipitates with R-β lactoglobulin. Since β-lactoglobulin and sheep serum are serologically unrelated, it is evident that the antibody was specifically directed against R.

Accurately known amounts of antibody‡ in 1.0 ml. of solution were placed inside small bags of sausage casing. These were dialyzed against an equal volume of a solution of *p*-hydroxyphenyl-R of accurately known concentration. The latter, in the outside solution, is a relatively small molecule, and, unlike the enormous antibody molecule, can pass through the dialytic membrane. Furthermore, this small molecule contains an R group and consequently can be specifically bound to antibody molecules inside the bag. Since this small molecule (hapten) contains an azo group, it is intensely colored and can, therefore, be accurately measured at low concentrations.

Dialysis was accelerated by slowly rocking these tubes, until equilibrium was established, i.e., the concentrations of dialyzable molecules were the same on both sides of the membrane. Now when tubes in which the bags contained merely buffered saline or bovine gamma globulin were compared with other tubes in which the bags contained the antibody solution, it was found, when equilibrium was reached, that the concentration of hapten in the outside solution of the former tubes was greater than in the case of the latter tubes. This means that the number of haptenic molecules that were free to pass back and forth across the membrane was reduced when antibody was present in one compartment of the tube; or, in other words, the antibody had bound some of the hapten and effectively removed it from the traffic across the membrane. In

*This grouping ($-N=N-C_6H_4-AsO_3H_2$) is hereafter referred to as R, following the terminology of Pauling, Pressman, et al.

†At acid pH the arsenate group (AsO_3H^-) combines with a proton and loses the negative charge which apparently is necessary for the binding of the antibody.

‡The concentrations of protein in the various antibody solutions were measured by ultraviolet-absorption spectroscopy.[18]

such experiments the number of antibody molecules inside the bag is known,* and the number of haptenic molecules bound to them can be readily calculated. The ratio of these 2 quantities, or r (i.e., $= \frac{\text{no. of moles. hapten bound}}{\text{total moles. antibody}}$) will vary with the concentration of free, i.e., unbound, hapten (c). The relationship between these two variables (r and c) is important because our objective is the determination of the value of r at an infinitely large concentration of hapten, i.e., we want to know how many haptenic molecules are bound to one antibody molecule when the latter is surrounded by an infinitely great concentration of

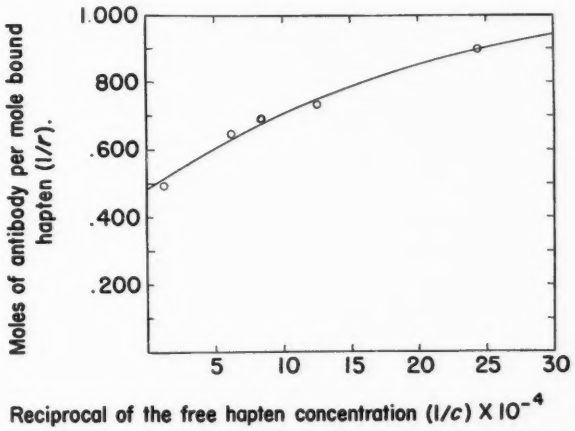


Fig. 2.—A plot of the reciprocal of r against the reciprocal of c (see text). The value of r when $1/c = 0$ is the binding capacity ("valence") of the antibody.

haptenic molecules. Under this circumstance, r becomes the binding capacity or "valence" of the antibody (or n). By carrying out a series of such dialyses at varying concentrations of hapten, one gets data that, plotted according to the relationship $\frac{1}{r} = \frac{1}{nkc} + \frac{1}{n}$, yield a curve† which may be extrapolated to give a limiting value of $1/r$ at infinitely large concentration of free hapten ($1/c = 0$), i.e., $1/n$.

As can be seen from Fig. 2, this particular sample of a precipitable rabbit antibody has a $1/n$ value of 0.50; hence n equals 2. This means that the average antibody molecule, at most, can combine with 2 haptenic molecules, or that, on the average, each antibody molecule has 2 specific binding sites.

This result provides strong support for the lattice theory. It is probable that the particular antibody under discussion can combine with 2 multivalent antigen molecules, and so participate in the type of aggregate formation envisioned by Marrack,[9] Heidelberger,[10] Pauling,[11] and their respective co-workers.

If, now, one accepts the lattice theory of precipitate formation, what are some of the implications for allergy that follow? For one thing, it follows that in cases of sensitivity to such drugs as aspirin, sulfonamides, penicillin, etc.,

*Calculated by assuming that the molecular weight of rabbit antibody is 160,000.[19]

†For a discussion of the significance of the shape of this and related curves, particularly as regards the deviation from linearity, see ref.[20]

one would not expect to form specific precipitates by mixing the antisera with the homologous "univalent" small molecule. In vitro attempts to detect and to measure serum antibodies against such molecules will have to resort to other procedures, i.e., binding studies of the type described above; or conversion of the univalent antigen to a multivalent particle by coupling to protein, or by adsorption on collodion particles, or by any other suitable procedure.

Another matter arising out of acceptance of the lattice theory concerns the usual failure to obtain precipitates with potent sensitizing antisera and homologous protein antigens, e.g., insulin,[21] egg albumin,[8] ragweed-pollen extract, etc. Since such protein antigens are highly likely to be multivalent, the failure of precipitates to form suggests that the antibody in these instances is univalent, or, if bivalent, that at least one binding site is "weak." The possibility that truly univalent antibodies exist has been suspected for a number of years.[5-8] However, unequivocal experimental demonstration of their existence has not yet been accomplished. Possibly the method for measuring the number of binding sites which has been described above will prove helpful in attacking this problem, and so, perhaps, help to shed light on the perplexing question as to whether "immune" antibodies and "sensitizing" antibodies are essentially the same, or whether they consistently differ in some property.

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DISCUSSION

DR. FREDERICH R. BROWN, New York, N. Y.—I think that Drs. Eisen and Karush have presented a very interesting method of studying antigen-antibody relationships. This is in the tradition of the quantitative studies of these reactions started by Heidelberger and his school. The data bear out the fact that antibodies against a single determinant are a heterogeneous mixture. This method is applicable to the studies of drug allergies in which the antigen may be a dialyzable substance. In this way our knowledge of simple chemical antigens which may be coupled to serum protein may be studied further, perhaps eliminating the need of biological testing. At the moment the more complex antigens such as ragweed pollen for which several antibodies have been demonstrated are not dialysable preventing their study by such precise methods. The presence of soluble specific compounds of ragweed antigen and thermostable antibody may explain the lack of correlation between the levels of thermostable antibody demonstrated in treated patients with the results of therapy because it requires a biological method of titration at the present time. It is conceivable that the ragweed antigen may be purified by more precise methods than used at present and this may allow a chemical method to be used in determining its binding by thermostable antibody.

EXPERIMENTALLY INDUCED INSULIN RESISTANCE AND ALLERGY IN THE RABBIT*

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INSULIN resistance occasionally develops in patients with diabetes, who may require as much as 1,000 to 5,000 units per day to control hyperglycemia. It is also seen in patients undergoing insulin-shock therapy for psychiatric disorders, and therefore, it may occur in the absence of diabetes. The unresponsiveness in most instances has remained unexplained. Infection, the commonest cause of increased insulin requirement, does not seem to account for resistance to insulin in most of the cases. Endocrine disturbances have been postulated, but again, with the exception of diabetes, they have rarely been demonstrated. Evidence has been presented that an immune mechanism plays a role in some cases of insulin resistance.[1-4] In a previous study,[2] it was demonstrated that responsiveness to human insulin was present in a patient who was highly resistant to crystalline (beef and pork) insulin; and, furthermore, the resistance seemed to develop during periods in which insulin was given and to disappear during periods in which insulin was withheld. This patient was also allergic to insulin. Injections of insulin caused swelling and generalized urticaria, and the serum contained skin-sensitizing antibody. However, allergy and resistance are not necessarily concomitant clinically, and in this patient the degree of resistance and hypersensitivity varied independently. These observations led to an attempt to induce insulin resistance on an immunological basis.

Twenty-four rabbits were injected repeatedly over a period of many months with 25 to 50 units of crystalline (beef and pork) insulin† incorporated into an adjuvant mixture,[5] containing mineral oil, Falba,‡ and killed acid-fast bacilli.§ Insulin tolerance tests were done in the fasting state with 0.1 μ/kg. given intravenously before immunization and at intervals thereafter. Table I summarizes the immunizing procedure in the 4 rabbits that became resistant and shows a comparison of the hypoglycemic effect of insulin before and after the development of resistance. Of the 19 rabbits similarly treated which did not become resistant, only 4 survived. Two died early in the course of the study because of overdosage with insulin; several died with diarrhea. Tuberculin-type hypersensitivity of high degree to one or more of the constituents of the adjuvant mixture may have been the cause of death in some of the others. In no case was there evidence of diabetes as judged by weight loss or hyperglycemia.

One of the rabbits (No. 5) was studied in detail, and the results obtained have been reported elsewhere.[6] A normal glucose tolerance test and the repeated

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†Kindly supplied by Dr. F. B. Peck of the Lilly Research Laboratories, Indianapolis, Ind.

‡Pfaltz and Bauer, Inc., New York, N. Y.

§*Mycobacterium butyricum*, kindly supplied by Dr. Jules Freund.

finding of a normal fasting blood sugar suggested that this animal had no resistance to his own insulin and that the resistance to injected insulin might be species-specific. Human insulin[7] given in a dose of 0.3 μ/kg. caused a fall in blood sugar equal to that seen in normal animals with a similar dose, whereas only a minimal fall followed the injection of larger doses of crystalline insulin. This indicated a clear-cut species difference in the resistance. Evidence was also obtained with cysteine-inactivated insulin,[8] indicating that the resistance was due to an antibody directed against antigenic determinants on the insulin molecule which were distinct from that portion of the molecule to which the hormone owes its hypoglycemic effect.

In none of the animals were there symptoms suggesting anaphylaxis, such as dyspnea, scratching, or collapse, following the injections of the adjuvant mixture or after testing with insulin intravenously. Nine months after resistance developed, the endermal injection of 0.02 ml. of crystalline insulin in a concentration of 4 μ/ml. on two occasions caused no immediate or delayed reactions in rabbit No. 5, the first to become resistant. Five months later, however, retesting with 0.1 ml. of insulin in a concentration of 8 μ/ml. caused a very definite delayed type skin reaction. Because of this result, the surviving animals in the series were tested at that time with human insulin and crystalline insulin. The results of these tests, as well as tests done in most of the animals with a filtrate of a heated culture of *Myco. butyricum* and also with Old Tuberculin, are shown in Table II. It will be noted that one of the resistant animals did not develop a cutaneous reaction to insulin and that several of the nonresistant animals did develop reactions. Thus, there was no

TABLE I

RABBIT NO.	INJECTIONS OF ADJUVANT MIXTURE: INTERVAL AFTER FIRST INJECTION*	INJECTIONS OF ADJUVANT MIXTURE: TOTAL NUMBER OF INJECTIONS	RESULTS OF INSULIN TOLERANCE TESTS: RELATION TO ONSET OF RESISTANCE	DOSE OF INSULIN (U/KG.)	BLOOD GLUCOSE MG./100 ML.					
						MINUTES AFTER INJECTION OF INSULIN				
					FBS	15	30	45	60	120
5	4 months	5	Before	0.1	118	100	98		113	113
			After	0.1	114	108	117		129	95
			After	0.5	96	94	84	84	85	94
24	8 months	3	Before	0.1	104	64	67		79	
			After	0.1	88	85	91		93	
			After	0.4	90	81	85	87	83	92
25	8 months	3	Before	0.1	83	80	78		65	
			Before	0.3	102	70	29	68	73	87
			After	0.1	80	90			94	
			After	0.4	95	116	92	102	92	97
26	8 months	3	Before	0.1	77	54	45		64	
			After	0.1	85		83			
			After	0.4	85	93	81	80	85	72

*Interval beween first injection of adjuvant mixture and observation of resistance.

correlation between resistance and cutaneous hypersensitivity to insulin. The skin reactions were slightly more prominent with crystalline insulin than they were with human insulin.

As shown in Table II, hypersensitivity to the Old Tuberculin and the filtrate of *Myco. butyricum* was variable. Material for testing was prepared by growing *Myco. butyricum* for one week at 37° C. in a fluid medium containing glycerine. Growth was rapid and profuse. The culture was autoclaved for 20 minutes at 15 pounds' pressure and passed through a Seitz filter. The filtrate was considered to be equivalent in concentration to Old Tuberculin 1:10. Skin tests were done with a 1:100 dilution of the filtrate and a 1:1000 dilution of Old Tuberculin. Strong cross reactions were seen, but the degree of tuberculin-type sensitivity was not correlated with the development of insulin resistance. Death of one animal (Rabbit No. 1) following skin tests with products of the two acid-fast organisms led us to omit these tests in animal No. 5.

TABLE II. RESULTS OF SKIN TESTS*

RABBIT	RESISTANCE	ANIMALS TESTED WITH			
		HUMAN INSULIN μ8	CRYSTALLINE INSULIN μ8	FILTRATE CULTURE M. BUTYRICUM	OLD TUBERCULIN 10^{-3}
1†	0			++	+++
4	0	+	++	0	0
5	++	+[a]	++ +[a]		
8	0			++	++
19	0			±	±
22	0	±	++	0	0
23	0	0	+	0	0
24	+			0	0
25	+	±[a]	+ +[a]	0	0
26	+		0	±	0
27	0	0	+	+	+
28	0			0	0
37	0	0	0	0	0
38	0			+	0

*Reactions read 48 hours after endermal injection of 0.1 ml.
†Died 72 hours after skin test.
[a]Tests with μ4 instead of μ8.

SUMMARY

1. Resistance to the hypoglycemic action of crystalline (beef and pork) insulin was induced in 4 of 24 rabbits by the repeated subcutaneous injection of this insulin incorporated in an adjuvant mixture.

2. Cutaneous hypersensitivity to insulin of the delayed type developed in 6 of 8 animals tested. This was not correlated with the development of resistance to insulin.

3. Skin reactions to crystalline insulin were more marked than those to human insulin suggesting some degree of species specificity.

4. Delayed skin reactions were observed following endermal injections of a filtrate of *Myco. butyricum* and Old Tuberculin.

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HYPERSENSITIVITY TO MERCUHYDRIN WITH POSITIVE SKIN TEST TO POST-TREATED MERCUHYDRIN SERUM*†

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MERCURIAL diuretics occupy a conspicuous role in the treatment of congestive heart failure. Finkelstein and Smyth[1] and Modell, Gold, and Clarke[2] have clearly demonstrated that Mercuhydrin produces excellent diuresis with minimal pain at the site of injection. Although many thousands of injections of this drug have been given without any adverse effect, there does exist a small number of patients who develop hypersensitivity to it. Intradermal tests with this product have failed to elicit a positive response. The following case report demonstrates the development of an allergic reaction to Mercuhydrin and an immediate wheal type of skin reaction to the serum of a previously treated patient with Mercuhydrin.

CASE REPORT

Mrs. F. O., a 42-year-old woman, was admitted to Bellevue Hospital on Oct. 30, 1947, with a diagnosis of mitral stenosis, interauricular septal defect (Lutembacher's disease), and congestive heart failure. There was no past or family history of any allergic disease.

Physical examination revealed a pale and poorly nourished white female in marked respiratory distress with moderate cyanosis. There was marked enlargement of the heart and a systolic thrill was palpable in the third left intercostal space. There was an early diastolic murmur and a rumbling systolic murmur at the apex. The rhythm was totally irregular and the first apical sound was accentuated. The blood pressure was 135/90 mm. There were many moist râles in both lung fields. The liver was enlarged 3 fingerbreadths below the costal margin and there was 3 plus edema of both lower extremities. The urinalysis and hemogram were within normal limits. The serology was negative and the sedimentation rate was 24 mm. per hour according to the Westergren method. The blood chemistry was normal. The electrocardiogram demonstrated auricular fibrillation with a right ventricular strain pattern. The roentgen-ray examination of the chest revealed a markedly enlarged heart with tremendous dilatation of the pulmonary artery and considerable engorgement of both lungs.

The patient was placed on a regular regime consisting of bed rest, digitalis, ammonium chloride, and a salt-free diet. There was a weight loss of 3¼ pounds in 4 days. On the fifth hospital day she received 2 c.c. of Mercuhydrin intramuscularly and thereafter daily injections were given until the fifteenth day of her hospital stay. There was a good therapeutic response as evidenced by a loss of 8 pounds in weight and marked improvement in her symptoms. On the sixteenth hospital day another dose of 2 c.c. of Mercuhydrin was given and in about one-half hour, the patient became markedly apprehensive, felt very chilly, and complained of heaviness in the chest, sweated profusely, and had a rise in temperature to 103.2° Fahrenheit. The following morning the fever receded somewhat and she was given another dose with a similar response. At this time it became apparent that a reaction to Mercuhydrin had occurred and it was decided to repeat the drug at a subsequent date. Ten days later, 2 c.c. were given by the same route and within 20 minutes the patient complained of palpitation, chills, choking sensation, and difficulty in breathing. One hour later there was a rise in temperature to 102.8° F. with the clinical picture of collapse. On the following day, the patient felt well again. On the thirty-fifth hospital day she received only 1 c.c. of Mercuhydrin intramuscularly and responded in a manner not unlike that following the administration of the larger dose. Several days later, 2 c.c. of Salyrgan, another mercurial diuretic, was injected intramuscularly without any unto-

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†Read before the Fifth Annual Meeting of the American Academy of Allergy, Atlantic City, N. J., December 6-8, 1948.

ward reaction. Subsequently, the patient continued to receive Salyrgan by the intramuscular route with an excellent diuretic effect and without any evidence of hypersensitivity (Fig. 1).

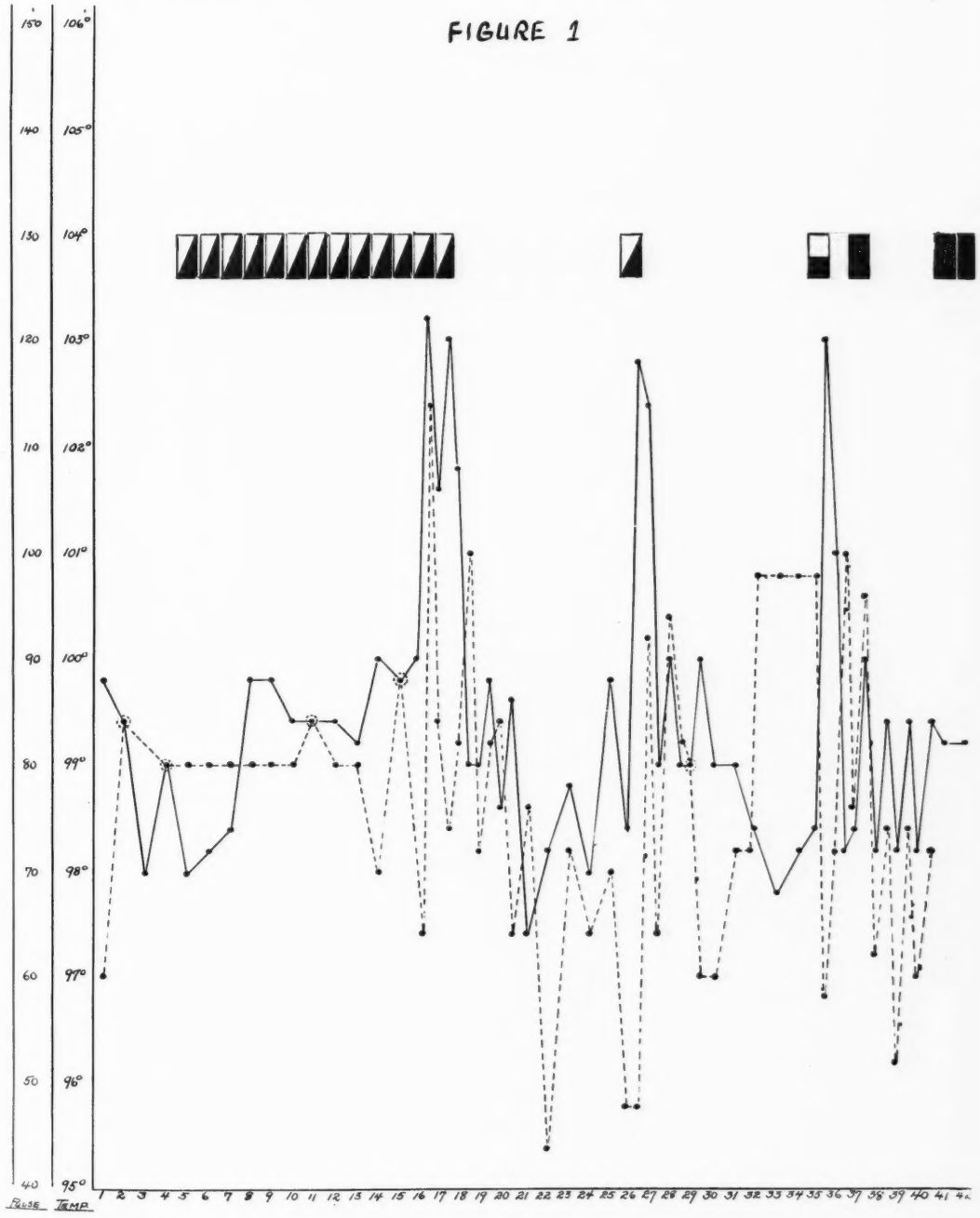


Fig. 1.

SKIN TEST STUDIES

Direct skin tests with concentrate ampule solution of Mercuhydrin and Salyrgan were performed with negative results (Fig. 2).

About 0.05 c.c. of blood serum obtained from another patient in congestive heart failure receiving Mercuhydrin without untoward reaction was injected intradermally into this hypersensitive patient, F. O. Within 10 minutes an immediate wheal type of reaction with considerable erythema and pseudopodia was noted. This became maximal in 15 to 20 minutes and thereafter continued to fade (Fig. 3).

Figure 2.

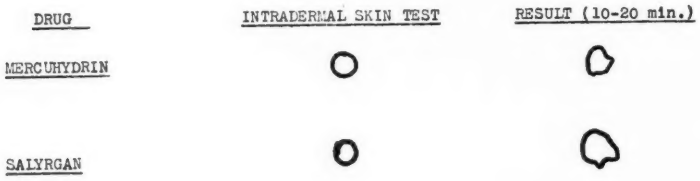
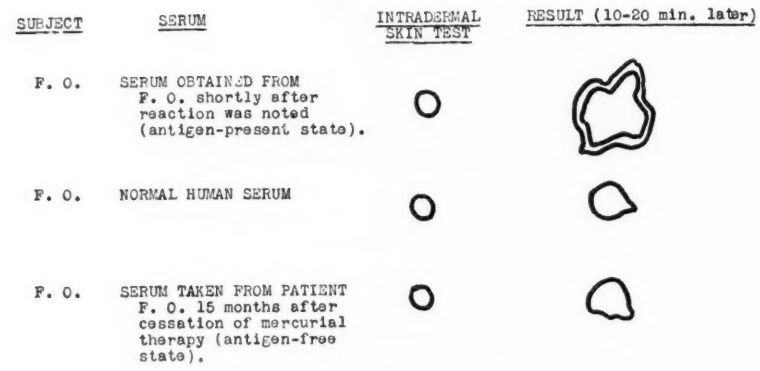


Figure 3.


SUBJECT
SERUM
INTRADERMAL SKIN TEST
RESULT (10-20 min. later)
F. O.
SERUM OBTAINED FROM F. O. shortly after reaction was noted (antigen-present state).
F. O.
NORMAL HUMAN SERUM
F. O.
SERUM TAKEN FROM PATIENT F. O. 15 months after cessation of mercurial therapy (antigen-free state).

Figs. 2 and 3.

As a control, .05 c.c. of normal human serum and .05 c.c. of serum taken from F. O. 15 months after the cessation of mercurial therapy (antigen-free state) were injected intracutaneously into F. O. A slight reaction with some erythema was noted in both instances (Fig. 3). The difference between the size of the control wheals and the size of the test wheal was 7 to 8 mm. in diameter and the marked pseudopodia observed with the test serum was absent in both control sera.

In addition, 10 cardiacs in congestive failure who had been receiving Mercuhydrin without any clinical manifestation of hypersensitivity to the drug, as well as an equal number of nonallergic normals not on mercurial therapy, were skin tested with 0.05 c.c. of serum taken from F. O. immediately following

the last injection of Mercuhydrin (antigen-present state). There was a slight increase in the wheal with some erythema, not unlike that noticed with normal human serum, in about 50 per cent of the individuals of either group. However, it should be emphasized that the degree of reaction observed with the controls mentioned previously was by no means equal in magnitude and extent to that noticed with the test serum.

Table I

DIRECT SKIN TESTS WITH SERUM ON CARDIACS
IN CONGESTIVE FAILURE WHO WERE TREATED WITH MERCUHYDRIN *
(clinically non-sensitive to Mercuhydrin)

PATIENT	INTRADERMAL SKIN TEST .05 cc.	RESULT 10-15 mins. later
1) O. J. **		
2) P. S.		
3) C. L.		
4) M. W.		
5) C. J.		
6) H. S.		
7) H. K.		
8) H. M.		
9) C. A.		
10) J. A.		

* The serum used was obtained from a patient shortly after treatment with Mercuhydrin without untoward reaction.

** Test was done shortly after reaction to Mercuhydrin appeared.

COMMENT

The reactions following the administration of mercurial diuretics have been adequately reviewed by many observers and may be classified into 4 main groups. First, there are those reactions that result from the disturbance in the water and electrolyte equilibrium of the body through excessive dehydration and diuresis. Second, there is the occurrence of sudden death apparently due to a direct effect of the mercurial upon the heart muscle producing ventricular tachycardia and ventricular fibrillation. Third, there are those symptoms

that result from the action of the mercurial ion per se such as stomatitis, hemorrhagic colitis, and renal irritation, and fourth, are the reactions due to hypersensitiveness to the drug. The development of gout, digitalis toxicity, spontaneous tetany, and precipitation of grand mal attacks in epileptic patients, have also been mentioned as toxic reactions following mercurial diuresis.

The fact that fever, tachycardia, chills, sweating, and collapse occurred in the above described patient after previous multiple well-tolerated injections, seems to favor an allergic reaction, in which the preliminary administration of the drug sensitized the patient, thus setting the stage for the outburst of the allergic response. Reducing the dosage of Mercuhydrin did not in any way alter the response of the patient; this is further evidence that the reaction was not due to a quantitative toxic effect of the drug but rather to a qualitative hypersensitive one.

Table II

NORMAL (NON-ALLERGIC) INDIVIDUALS — NOT TREATED WITH MERCUHYDRIN

PATIENT	SERUM	INTRADERMAL SKIN TEST .05 cc.	RESULT 10-15 mins. later
1) S. L.	SERUM OBTAINED FROM F. O. shortly after last injection of Mercuhydrin (antigen-present state)		
2) L. F.	"		
3) H. S.	"		
4) N. M.	"		
5) H. P.	"		
6) M. W.	"		
7) S. S.	"		
8) A. S.	"		
9) M. M.	"		
10) J. G.	"		

Kaufman,[3] in reviewing the literature on the causes of sudden death following the injection of various mercurial diuretics, found that up to 1947 there were 31 recorded cases to which he added one of his own, bringing the total to 32. In all these instances the intravenous method was employed solely, and at no time was there a death reported following other methods of application. Inasmuch as the drug was given intramuscularly in this case, it was felt safe to continue despite the reactions noted.

The demonstration of positive skin tests in drug allergy has not met with uniform success by various workers in this field. The European literature contains many references, but in this country most authorities have failed to cor-

roborate their results. However, a few exceptions do exist, for in 1938 Kern[4] described a case of rhinitis and bronchial asthma due to pthalic anhydride with positive scratch test and passive transfer. In 1945, Feinberg and Watrous[5] reported similar cases of asthma and rhinitis in workers exposed to Halazone and chloramine T. who demonstrated skin antibodies. With the advent of chemotherapeutic agents such as the sulfonamides and penicillin, many cases of acquired sensitivity to these compounds have appeared in the literature. Although occasional positive skin tests were reported, in most instances the scratch and intracutaneous tests were negative.

Whittemore and De Gara,[6] in 1946, reported a case of marked clinical sensitivity to sulfadiazine and sulfathiazole in whom positive scratch tests to sulfadiazine and sodium sulfathiazole were present. Sherman and Cooke[7] in 1947 demonstrated the presence of a skin sensitizing antibody in a patient who had a severe reaction to sulfadiazine.

Leftwich,[8] in 1944, was unable to obtain positive skin tests with solutions of various sulfonamide drugs in cases of sulfonamide hypersensitivity. However, when he employed blood sera from persons receiving sulfonamide medication in doses adequate to produce an effective blood level, a positive intradermal test was noted. Subsequently Fink, Burton, and Wheeler,[9] while working with children and employing the same method, obtained negative results. Sherman and his group[10] were also unable to duplicate the results that Leftwich obtained in patients known to be sensitive to sulfadiazine.

Fox, Gold, and Leon[11] in 1942 reported a case of hypersensitivity to mercurials in whom scratch tests with ampule solutions of Mercupurin and Salyrgan failed to elicit a positive response. In our case, similar results were obtained employing the intradermal technique. Burrows and Stokes[12] obtained a positive patch test in several cases of erythematous eruptions following repeated injections of Neptal, a mercurial closely related to Salyrgan. Gottlieb[13] recently encountered a hypersensitive reaction to Mercupurin with urticaria in whom the patch-scratch test elicited a sharply demarcated swelling with moderate erythema.

The marked intradermal reaction with pseudopodia demonstrated in this hypersensitive patient with serum obtained from an individual treated with Mercuhydrin without untoward reaction indicates that occasionally a skin reaction with serum conjugate may occur in drug hypersensitivity. However, the reaction must be interpreted quantitatively, since frequently, normal serum in itself may elicit a slight positive response. Its practical application awaits further study.

SUMMARY

1. A case of mitral stenosis with interauricular septal defect in congestive failure, in which hypersensitivity to Mercuhydrin developed, is presented.

2. Substitution of another mercurial, Salyrgan, was well tolerated.

3. Direct skin tests with ampule solution of Mercuhydrin and Salyrgan were negative.

4. A positive skin reaction with marked erythema and pseudopodia was elicited in the Mercuhydrin-sensitive patient, with the blood serum taken from another patient previously treated with Mercuhydrin.

5. Normal human untreated serum and serum obtained from the above patient in the antigen-free state (15 months after cessation of Mercuhydrin therapy) were employed as controls with only a slight wheal and erythema.

6. Ten cardiacs in congestive failure treated with Mercuhydrin, as well as an equal number of nonallergic normal individuals not receiving the drug, were tested intradermally with serum taken from the patient presented in the antigen-present state (immediately after last injection of Mercuhydrin). A slight positive reaction similar to that observed with normal serum was noted in about one-half the cases of either group. However, the size of the wheal in all of the controls was 7 or 8 mm. less than the test wheal.

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Original Articles

THE EFFECT OF INHALATION OF ANTIGENS BY THE GUINEA PIG ON THE PRODUCTION OF ANAPHYLAXIS*

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INTRODUCTION

THE production of rhinitis and asthma in guinea pigs by direct intranasal instillation or vaporization of the antigen was reported as early as 1916.[1, 2] Since then this problem has been studied by many other workers.[3-6] Notable among these is the exhaustive study of Ratner and his co-workers.[7-10] They were able to induce sensitivity and anaphylaxis in guinea pigs by the inhalation of horse dander antigen. Some workers tested for sensitivity by intravenous injection of antigen following primary sensitization by inhalation. Others used the reversed procedure. The production of anaphylaxis by both methods was reported. In comparison to the conventional methods of sensitization in animals, the use of inhaled antigen both for the sensitization and production of shock would seem to be more closely allied to allergy in man. For this reason the latter method was used in the studies to be described.

METHODS

A special box was constructed of wood and glass measuring one foot in all dimensions. The top and two of the sides were of glass set in a wooden frame. A door was inserted into one side. An inlet was bored through one of the wooden walls and an outlet cut in the same site of the opposite wall. The inner and outer surfaces of the outlet were covered by a fine metal wire mesh and cotton wool placed between them to serve as a filter. The spout of a No. 40 de Vilbis nebulizer was fitted through the inlet. The nebulizer was in turn connected to a compressed air outlet by rubber tubing. All connections were reinforced by bound wire.

The antigens used were ragweed pollen powder and extract, and horse dander powder and extract.† The antigenic material was placed in the lower half of the nebulizer. A constant amount was not used, but sufficient material was kept in the nebulizer to maintain an adequate concentration of antigen in the box as judged by the visual dust or vapor clouds. The compressed air was then blown through the system for varying periods as indicated in the tables. A cloud of dust or a fine spray of fluid was maintained in the box during the entire period of exposure.

A total of 85 young guinea pigs of both sexes were used. They were unselected, weighing between 250 and 400 grams, and kept on a normal diet in a constant cage environment. The study was carried out from October, 1947,

*From the McGill University Clinic, Royal Victoria Hospital, Montreal, Quebec.

†The ragweed pollen powder was obtained through the courtesy of Desbergers Ltd. of Montreal. The ragweed extract and horse dander extract, both 1:100 dilution strength, were the commercial preparation of Abbott. The horse dander powder was prepared as described by Ratner.[10] Ragweed 1:100 – 0.070 mg. total nitrogen/c.c.; horse dander 1:100 – 0.014 mg. total nitrogen/c.c.

to April, 1948. Exposure gave rise to symptoms of mild excitement, mild dyspnea and rubbing of the nose in most instances. These are referred to a 1 plus in the tables. Symptoms of a more marked nature, such as marked excitement and marked dyspnea are referred to as 2 plus, while 3 plus denotes symptoms going on to collapse. The same grading is used in the tables to indicate the symptoms elicited by intravenous injection.

The histamine content of the blood was determined by the method of Barsoum and Gaddum as modified by Code.[12, 13, 14] The mean histamine level of the blood in guinea pigs is 0.133 γ/c.c. rising from 2 to 13 times the original level following anaphylactic shock, as shown by Code in 1939.[15, 16]

RESULTS

Experiment I.—A group of 10 animals were exposed to ragweed pollen powder inhalation for 30-minute periods daily for 6 days. Re-exposure was repeated on the seventeenth, twenty-seventh, and twenty-ninth experimental days. The only results were mild symptoms on the seventeenth, twenty-seventh, and twenty-ninth days.

Experiment II.—A second group of 10 animals were exposed to ragweed pollen powder antigen. Daily inhalation of 30 minutes' duration was carried out for 7 days. The animals were re-exposed on the thirteenth, fourteenth, and fifteenth experimental days. No symptoms were elicited in any of the exposures in this experiment.

Experiment III.—Ten animals were subjected to 30 minutes' daily exposure of 1:100 dilution of ragweed pollen extract for 6 days, then re-exposed on the seventeenth, twenty-first, and twenty-second experimental days. The only symptoms noted were those of a mild nature and a 1 plus reaction, which were seen on the twenty-first and twenty-second days.

Experiment IV.—Ten animals were exposed for 30 minutes daily for 20 days to a 1:100 dilution of horse dander extract. One animal was then sacrificed and blood taken for blood histamine determinations. The animals were again exposed on the thirty-third day. A second animal was then sacrificed and blood taken for histamine determination. The remaining 8 animals were again exposed on the thirty-fourth, thirty-fifth, thirty-sixth, thirty-seventh, and forty-seventh day. On the forty-seventh day 3 of the animals were injected intravenously via the jugular vein with 1 c.c. of 1:100 dilution of horse dander extract. The vein was first exposed by dissection in the unanesthetized animal. Blood was taken via the intracardiac route from one of these animals, just prior to and immediately after the intravenous injection for blood histamine determination. The remaining 5 animals were again exposed on the forty-ninth day. The results are summarized in Table I.

These animals began to show mild symptoms of restlessness and dyspnea after the fourteenth day of exposure. However, none of the animals showed symptoms of collapse. The blood histamine following exposure on the twentieth day was 0.138 γ/c.c. whole blood, while that on the thirty-third day was 0.175 γ/c.c., well within normal limits. The 3 animals which had been

injected intravenously on the forty-seventh day suffered severe, nonfatal anaphylactic shock consisting of dyspnea, sneezing, spasm, convulsions, and finally unconsciousness. It was first believed that this represented true anaphylactic shock because of previous sensitization by inhalation. However, as later studies will show, the same result was obtained in fresh unexposed animals. Therefore, the above results cannot be accurately judged because they may be either anaphylactic or anaphylactoid shock. The blood histamine before injection was 0.16 γ/c.c. and 0.108 γ/c.c. after injection.

TABLE I. HORSE DANDER EXTRACT ANTIGEN

NO. OF ANIMALS	EXPERIMENTAL DAY	TIME OF EXPOSURE	SYMPTOMS (EACH DAY)	BLOOD HISTAMINE γ/C.C.
10	1 to 13 days (incl.)	30 min. (q.d.)	– (100%)	
10	14 to 19 (days incl.)	30 min. (q.d.)	+ (100%)	
10	20	30 min. (q.d.)	+ (100%)	0.138
9	33	30 min. (q.d.)	+ (100%)	0.175
8	34	30 min. (q.d.)	+ (100%)	
8	35	30 min. (q.d.)	– (100%)	
8	36	30 min. (q.d.)	– (100%)	
8	37	30 min. (q.d.)	– (100%)	
8	47	30 min. (q.d.)	– (100%)	
3	47	i.v. injection	+++ (100%)	Before injection: 0.16
5	49	i.v. injection	+ (100%)	After injection: 0.108

\+ = Mild excitement, dyspnea, and rubbing of the nose.
++ = Marked excitement and dyspnea.
+++ = Collapse.
% = Number of animals showing symptoms.
– = No symptoms.

Experiment V.—Twenty animals were exposed to horse dander powder antigen for 30 minutes daily for 20 days. Ten of these animals were then injected subcutaneously daily with 200 γ of thyroxin diluted in 0.2 c.c. of distilled water for 10 days. Daily subcutaneous injections of 0.2 c.c. of distilled water alone for 10 days were given to the remaining 10 animals. After this period, i.e., the thirtieth day, 4 animals of each group were given an intravenous injection of 1 c.c. of 1:100 dilution of horse dander, 2 of each group by the jugular vein and 2 via the intracardiac route. Blood samples for histamine determination were taken before shock by cardiac puncture and after shock by venesection. On the thirty-seventh day, one animal of each group was subjected to a 2-hour continuous exposure. The results are summarized in Table II.

The 20 animals began to show mild symptoms from the tenth day on. Intravenous injection of the antigen on the thirtieth day produced acute nonfatal anaphylaxis of a similar degree in all animals of both groups. Since it has been shown that the administration of thyroxin to sensitized animals increases their susceptibility to anaphylaxis following injection of the shock dose, it was thought that a difference might be demonstrated between the thyroxin treated group and their controls.[11] It was impossible to determine whether the symptoms in one group were more severe than those in the other.

The blood histamine of one animal of each group before and after injection also failed to show a rise of blood histamine as seen in anaphylactic shock, being:

	CONTROL	THYROXIN
Histamine	Before: 0.11 γ/c.c. After: 0.04 γ/c.c.	Before: 0.14 γ/c.c. After: 0.145 γ/c.c.

The 2-hour exposure on the thirty-seventh day following both inhalation exposure and intravenous sensitization failed to give rise to symptoms of anaphylaxis.

TABLE II. HORSE DANDER POWDER ANTIGEN

NO. OF ANIMALS	EXPERIMENTAL DAY	PROCEDURE	SYMPTOMS	BLOOD HISTAMINE γ/C.C.
		Thyroxin Animals		
10	1 to 10 (days incl.)	30 min. exposure	– (100%)	
10	10 to 20 (days incl.)	30 min. exposure	+ (100%)	
10	20 to 30 (days incl.)	200 thyroxin s/c	– (100%)	
4	30	i.v. injection antigen	+++ (100%)	Before: 0.14 After: 0.145
1	37	2 hr. exposure	– (100%)	
		Control Animals		
10	1 to 10 (days incl.)	30 min. exposure	– (100%)	
10	10 to 20 (days incl.)	30 min. exposure	+ (100%)	
10	20 to 30 (days incl.)	0.2 c.c. H_2O s/c	– (100%)	
4	30	i.v. injection antigen	+++ (100%)	Before: 0.11 After: 0.04
1	37	2 hr. exposure	– (100%)	

\+ = Mild excitement, dyspnea, and rubbing of nose.
++ = Marked excitement and dyspnea.
+++ = Collapse.
% = Number of animals showing symptoms.
– = No symptoms.

Experiment VI.—Twenty guinea pigs were initially injected with 1 c.c. of a 1:100 dilution of horse dander extract, 15 via the jugular vein and 5 via the intracardiac route. Blood for histamine determination was taken from one animal immediately prior to and after the injection. Ten of these animals were then injected subcutaneously daily for 10 days with 200 γ of thyroxin in 0.2 c.c. distilled water. The remaining 10 were injected with 0.2 c.c. of distilled water alone. On the twelfth day, both groups, i.e., the group treated with thyroxin and the control group treated with distilled water, were subjected to one-hour inhalant exposure of horse dander powder. Blood from one animal of each group was taken for histamine level immediately following the exposure. Three animals of the control group and 3 of the thyroxin-treated group were again re-exposed on the fifteenth and twenty-second days. Table III gives a summary of the results.

All animals showed signs of varying degrees of acute shock consisting of dyspnea, spasm, convulsions, and unconsciousness, following primary intravenous and intracardiac injection. The blood histamine in one of these animals was 0.42 γ/c.c. before and 0.125 γ/c.c. after injection. These are not

the figures usually found in acute anaphylactic shock. Inhalant exposure on the twelfth day for one hour of both groups of animals, i.e., the thyroxin-treated group and the controls, produced only signs of mild dyspnea. None of the animals in either group exhibited signs of even mild collapse. Blood histamine taken immediately after exposure in one animal of each group was not remarkable, the control being 0.10 γ/c.c. and thyroxin 0.09 γ/c.c. The 3 animals of each group re-exposed on the fifteenth and twenty-second days showed only minimal symptoms of dyspnea.

TABLE III. INTRAVENOUS SENSITIZATION

NO. OF ANIMALS	EXPERIMENTAL DAY	PROCEDURE	SYMPTOMS	BLOOD HISTAMINE γ/C.C.
		Thyroxin Animals		
10	1	i.v. injection antigen	+++ (100%)	
10	2 to 11 (days incl.)	200 thyroxin s/c	– (100%)	
10	12	1 hr. exposure	+ (100%)	0.09
3	15	2 hr. exposure	+ (100%)	
3	22	1 hr. exposure	+ (100%)	
		Control Animals		
10	1	i.v. injection antigen	+++ (100%)	Before : 0.42 After : 0.125
10	2 to 11 (days incl.)	0.2 c.c. H_2Os/c (q.d.)	– (100%)	
10	12	1 hr. exposure	+ (100%)	0.10
3	15	2 hr. exposure	+ (100%)	
3	22	1 hr. exposure	+ (100%)	

\+ = Mild excitement, dyspnea, and rubbing of nose.
++ = Marked excitement and dyspnea.
+++ = Collapse.
% = Number of animals showing symptoms.
– = No symptoms.

TABLE IV. PROLONGED EXHALANT EXPOSURE

NO. OF ANIMALS	EXPERIMENTAL DAY	PROCEDURE	SYMPTOMS
5	1	5 hour exposure	+ (100%)
5	12	5 hour exposure	– (100%)

\+ = Mild excitement, dypsnea, and rubbing of the nose.
% = Number of animals showing symptoms.

Experiment VII.—Although Ratner[10] states that antianaphylaxis rarely occurs as a result of inhalant exposure, it was thought that this possibility should be investigated in view of the consistently negative findings recorded above. Five guinea pigs were given a single exposure to horse dander powder for 5 hours. After an interval of 12 days, the animals were re-exposed to the same antigen. The results, as shown in Table IV, were again negative.

DISCUSSION

Acute anaphylaxis was not produced by inhalant means using ragweed pollen or horse dander in the powdered or fluid form, as antigen, after prolonged exposure. The symptoms noted were dyspnea and restlessness but collapse was not observed following any of the inhalant exposure studies. The period between exposures was varied, ranging from a few days to a few weeks. This should cover the range of incubation times necessary for hypersensitivity to be present. The results following intravenous injection of the antigen

cannot be classified as anaphylaxis since the symptoms elicited by this means in the fresh unexposed animals were almost identical to those in the exposed groups. Rather, the symptoms would appear to be those of anaphylactoid shock. The injection of thyroxin over a 10-day period failed to exercise the desired effect of lowering the animals' resistance to either inhaled or injected antigen.[11]

The preparation of the antigen may be a factor in the failure to produce anaphylaxis. However, the ragweed pollen, both extract and powder, as well as the horse dander extract was obtained from reliable commercial houses. The horse dander was prepared according to the method of Ratner. The size of the particles was not measured, but a fine spray of powder was maintained in the box during the exposure. The use of the nebulizer seemed an excellent method of delivering either the liquid or dust particles. The animals used were unselected young guinea pigs obtained from dealers and were not of any particular strain or sex. This might be one of the reasons for the inability to produce anaphylaxis.

These experiments do not consist of a refutation of other observers. However, they do indicate that in the experimental animal at least, hypersensitivity as induced by this means is not consistent. Other workers have also been unable to obtain positive results by inhalation, using horse dander, dry pollen, and dry horse serum.[17, 18] The results are not in accord with those published by Ratner[10] but the reasons seem obscure. There are, however, several possible explanations. It may be that different strains of animals may vary in their capacity to become sensitive as a result of an antigenic stimulus of this nature. In the few animals in which blood histamine determinations were made, the changes observed did not correspond to those usually found in acute anaphylaxis in this species. It furthermore has been well established that the injection of thyroxin to sensitized guinea pigs as well as normal rats markedly increases the sensitivity of the former to anaphylactic shock and the latter to the egg white reaction.[11, 19] Both of these syndromes depend in part on histamine liberation. It was expected that even though the methods employed were only capable of inducing limited antibody formation, that thyroxin injection should have at least intensified the result. Since even this was not observed, it seems likely that hypersensitivity was not induced in the animals used by the above methods.

SUMMARY

1. A method for delivering an anigen by the inhalant route is described.

2. Experiments using ragweed pollen powder and fluid antigen, and horse dander powder and fluid antigen by the inhalant route failed to produce satisfactory symptoms of anaphylaxis in guinea pigs.

3. The injection of thyroxin did not lower the threshold of susceptibility to anaphylaxis of guinea pigs to inhalant exposure.

4. Although primary intravenous injection of guinea pigs with fluid antigen was performed, inhalant exposure after a suitable incubation period failed to give rise to symptoms of anaphylaxis.

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STUDIES IN BACTERIAL ALLERGY*†

II. Preparation of Crude Nucleoprotein and Polysaccharide Fractions of Bacteria

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NUCLEOPROTEIN and polysaccharide fractions have been studied more extensively than other components of bacterial cells. Early studies in this series will be limited to these two fractions.

Acid precipitation of nucleoprotein and alcohol precipitation of polysaccharide were the basis of methods used by Zinsser and Parker,[1] Julianelle and Hartmann,[2] Lancefield,[3] Heidelberger and Avery,[4] Tomczik,[5] and others. The following modification of their techniques has been used to prepare crude polysaccharides and nucleoproteins of *Streptococcus haemolyticus, Streptococcus viridans, Streptococcus faecalis, Staphylococcus aureus, Staphylococcus albus,* Friedländer's bacillus, *Pseudomonas pyocyanea, Bacillus coli, Bacillus aerogenes, Micrococcus catarrhalis, Hemophilus influenzae* and *Hemophilus pertussis.*

METHOD

Add 5.0 ml. of pure broth culture of organism to be fractionated to each of 10 or more 5-liter flasks of trypticase broth or other suitable media. Incubate 18 to 24 hours. Harvest organisms in Sharples centrifuge. Suspend bacterial sediment in 5 liters of physiologic saline, to get rid of culture medium. Harvest again in Sharples centrifuge. Transfer sedimented bacteria to cryochem apparatus. Apply negative pressure until bacterial sediment froths. Freeze and dry. Transfer dried bacteria to a metal can with screw top. Add steel ball bearings of 2 or 3 different sizes (e.g., ⅜″, ½″, ⅝″). Rotate mechanically for 8 to 24 hours in the cold. Extract powdered bacteria with N/100 NaOH, 1 liter to each 50 liters of original culture, in icebox overnight or longer. Shake frequently. Exercise utmost care to minimize contamination and to prevent growth of contaminants.

A. Nucleoprotein is precipitated from NaOH extract at pH 2.0 to 4.0 with dilute acetic acid. Redissolve in N/100 NaOH. Reprecipitate with acetic acid 2 or more times. Dry precipitate in cryochem apparatus, weigh, redissolve in Coca's solution adjusted to pH 8.3 with weak NaOH. Save supernates. Keep cold at all times.

B. Evaporate acid supernates from *A* on water bath to approximately 50 milliliters. Precipitate in cold with 10 volumes of 95 per cent alcohol. Redissolve in water adjusted to pH 4.0 with dilute acetic acid. Reprecipitate with alcohol twice or until all precipitate redissolves in acid. Wash precipitate with equal parts of alcohol and acetone. Dry, weigh, and dissolve in Coca's solution.

These crude polysaccharide fractions give strongly positive Molisch reactions.

Nucleoproteins and polysaccharides in arbitrary concentrations can be used for anaphylaxis experiments and for skin testing.

*This is one of a series of studies supported by a grant from Ciba Pharmaceutical Products, Inc., Summit, N. J.

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DISCUSSION

Bacterial fractions made in this way are crude. The terms "nucleoprotein" and "polysaccharide" conform to those given similar preparations by Zinsser and Parker,[1] Tomczik,[5] Julianelle and Hartmann,[2] and others.

Polysaccharide fractions can be extracted from whole organisms by boiling in acid at pH 2.0 or by the formamide method of Fuller.[6] Both methods denature the nucleoproteins.

Nucleoprotein fractions prepared from fluid growth media have been used widely in the diagnosis of tuberculosis, brucellosis, and histoplasmosis. Polysaccharides have also been prepared from this source.[7] The method described is not designed to yield pure protein and polysaccharide fractions. It separates heat-coagulable, acid-insoluble proteins from heat-resistant, acid-soluble polysaccharides. Protein antigens which are insoluble in alcohol and soluble in acid, or are resistant to heat (e.g., "B" protein of *Staph. aureus*[8] and the M[9] and X[10] antigens of Group A hemolytic streptococcus) require other methods of separation from polysaccharides. On the other hand, at least one polysaccharide, pneumococcus type 1, is precipitated by acid with the nucleoprotein.[11] The problems are much more complex than these simple examples indicate. They are being studied.

SUMMARY

A method is described for the separation of crude soluble nucleoprotein and polysaccharide fractions from a wide variety of bacteria.

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STUDIES IN BACTERIAL ALLERGY*†

III. Results of 3860 Cutaneous Tests With 34 Crude Polysaccharide and Nucleoprotein Fractions of 14 Different Bacteria

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With the Technical Assistance of Peggy Jean Radford, M.T., and Jean Foster, B.A., R.N.

DIAGNOSTIC cutaneous tests with bacterial vaccines in allergic patients have been advocated,[1-4] and decried.[5-7] Diagnostic cutaneous reactions result from the interaction of sensitized tissue with soluble specific extrinsic antigen. Vigorous chemical treatment is required in vitro to separate the complex intact bacterium into its soluble antigenic components. Any discussion of cutaneous reactions to bacterial antigens seems futile if these basic facts are ignored. Polysaccharide fractions of bacteria have been shown to cause anaphylactic shock, contraction of the sensitized uterus in animals,[8-12] and the immediate wheal-type of cutaneous reaction in man.[13, 14] The nucleoprotein fractions produce delayed tuberculin-type cutaneous reactions in human tuberculosis, Brucellosis, histoplasmosis, and in animals made allergic by infection or immunization.[15-17] Under proper conditions the nucleoprotein may produce anaphylactic shock in animals.[18] Stevens and Jordani[21] reported immediate and delayed reactions to intracutaneous tests with nucleoproteins of 5 respiratory organisms in 100 consecutive asthmatics.

Kraft, Mothersill, and Nestmann[22] reported the results of intracutaneous tests in allergic patients with extracts of fragmented bacteria. There are numerous references to the use of vaccines and extracts of dried bacteria.[1-4, 19, 20] This is the first report of a large series of cutaneous reactions to the polysaccharide and nucleoprotein fractions of a variety of organisms. Most of the patients were tested as part of an allergy investigation. Many had rheumatism. Many had no obvious infection. Many had obvious infections which were possible sources of bacterial allergy. The clinical diagnosis was correlated with cutaneous reactions in 36 selected cases (Table III).

Intracutaneous Tests.—Table I contains a summary of the immediate and delayed cutaneous reactions to 23 polysaccharide and 11 nucleoprotein fractions of 14 different species of bacteria. No effort was made to identify types, groups, or strains of the species used; 3860 tests were tabulated. The largest number of tests with any fraction was 221. The numbers in parentheses after the names of the bacteria refer to different strains of organisms or to modifications in preparation of the fractions. Cutaneous tests preceded intracutaneous tests in every case, as a precaution against systemic reactions. Only intracutaneous tests are shown in Table I.

*This is one of a series of studies supported by a grant from the Ciba Pharmaceutical Products, Inc., Summit, N. J.

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The largest number and the highest percentage of wheals were elicited by polysaccharides of *Streptococcus fecalis* (5) and *Staphylococcus aureus* (35). Other frequent excitants of wheals were the polysaccharides of staphylococcus (A), (7), (10), (20); *B. aerogenes* (G), (13); *Streptococcus hemolyticus* (19); *Micrococcus catarrhalis* (24); and *Streptococcus fecalis* (11).

Streptococcus fecalis (L) and *Streptococcus hemolyticus* (19) polysaccharides elicited the highest percentage and the largest number of delayed re-

TABLE I.*—SUMMARY OF 3860 INTRACUTANEOUS TESTS WITH 23 POLYSACCHARIDE AND 11 NUCLEOPROTEIN FRACTIONS OF 14 SPECIES OF BACTERIA

BACTERIA	TOTAL TESTS	IMMEDIATE REACTIONS				DELAYED REACTIONS			
		1+	2-3+	4+	TOTAL	1+	2-3+	4+	TOTAL
Aerogenes CHO†(13)	221	30	4	0	34	28	4	0	32
Aerogenes CHO(G)	62	32	14	0	46	10	18	8	36
Coli CHO(14)	221	23	5	0	28	17	7	1	25
Friedländers CHO(27)	166	9	6	1	16	10	4	0	14
Influenzae CHO(22)	55	10	1	1	12	13	6	1	20
Influenzae CHO(C)	54	21	6	1	28	17	13	5	35
Micrococcus CHO(24)	218	36	6	0	42	63	19	2	84
Pneumococcus									
Type I CHO(F)	37	19	5	0	24	7	6	2	15
Type I NP‡(I)	50	3	3	0	6	1	2	1	4
Pertussis CHO(E)	55	20	8	0	28	3	5	0	8
Pertussis NP(H)	57	4	0	0	4	7	5	0	12
Pyocyanea CHO(17)	218	21	3	0	24	62	22	4	88
Pyocyanea CHO(K)	63	14	0	0	14	13	6	0	19
Pyocyanea NP(39)	96	7	0	0	7	16	6	1	23
Pyocyanea NP(D)	50	2	1	0	3	0	0	0	0
Staphylococci									
Aureus Hemo CHO(35)	73	33	13	0	46	18	20	5	43
Aureus Hemo CHO(A)	67	28	26	1	55	8	14	5	27
Aureus Hemo CHO(10)	148	21	12	0	33	9	7	2	18
Aureus Hemo NP(12)	55	0	0	0	0	0	0	1	1
Aureus Hemo NP(43)	90	16	2	0	18	21	20	7	48
Albus Hemo CHO(7)	221	32	6	0	38	10	3	2	15
Albus Hemo CHO(44)	89	5	0	0	5	5	2	0	7
Albus Hemo NP(20)	215	27	9	1	37	38	32	12	82
Albus Hemo NP(41)	94	8	2	0	10	24	12	6	42
Albus Hemo NP(42)	94	11	1	0	12	16	13	7	36
Streptococci									
B. Hemolytic CHO(B)	52	21	3	0	24	4	1	0	5
B. Hemolytic CHO(19)	206	32	11	2	45	55	52	45	152
B. Hemolytic NP(47)	52	8	1	0	9	17	5	0	22
Fecalis CHO(5)	221	67	15	0	82	6	0	1	7
Fecalis CHO(L)	55	29	4	0	33	8	8	26	42
Fecalis NP(40)	94	6	1	0	7	14	3	1	18
Viridans CHO(J)	54	18	4	0	22	6	1	0	7
Viridans CHO(11)	221	23	5	0	28	5	4	0	9
B. Subtilis CHO(30)	136	7	1	1	9	4	4	0	8
Totals	3860	643	178	8	829	535	324	145	1004

*The formamide method of Fuller[25] was used in the preparation of the polysaccharides of *Staph. aureus* (A), (10), *Str. fecalis* (5), *Str. viridans* (11), *Staph. albus* (7), aerogenes (13).

The method outlined in Study II was used in preparing the polysaccharides: *Staph. aureus* (35), *Str. hemolyticus* (19), (36), *Staph. albus* (44), and pyocyanea (17).

The polysaccharides of aerogenes (G) and coli (14) were obtained by digesting the organism in concentrated sodium hydroxide.

The nucleoprotein fractions were precipitated from N/100 NaOH extracts of ground bacteria by acid at pH 4.0 in *Str. hemolyticus* (47), pyocyanea (39), *Str. fecalis* (40), and at pH 2.0 in *Staph. albus* (41), (42), *Staph. aureus* (43).

†CHO = Polysaccharide.

‡NP = Nucleoprotein.

actions. Delayed reactions were elicited frequently, also, by the nucleoproteins of staphylococcus (20), (41), and (43), and the polysaccharides of *Micrococcus catarrhalis* (24) and *Pseudomonas pyocyanea* (17).

The polysaccharide fractions elicited more immediate than delayed reactions as a rule. Exceptions were influenzae (22) and (C), micrococcus (24), pyocyanea (17) and (K), and *Str. fecalis* (L). These 6 exceptions were responsible for 346 (45.3 per cent) of the 764 delayed reactions elicited by polysaccharides. Seven hundred thirteen (24.6 per cent) of the 2913 polysaccharide tests resulted in immediate wheal reactions. They were widely distributed among the polysaccharides listed.

Staph. aureus (12) and pyocyanea (D) nucleoproteins were the poorest reactors. All of the other fractions elicited immediate or delayed skin reactions in 14 to 76 per cent of persons tested. There were 829 immediate wheal reactions, 21.5 per cent of the total 3860 tests. Eight (1 per cent) were large, 4 plus; 178 (21.6 per cent) were graded 2 plus to 3 plus. There were 13 positive cutaneous (scratch) tests (Table III).

There were 1004 delayed reactions, 26.0 per cent of the total tests. Most of these reached their maxima at 20 to 24 hours. Forty-eight-hour reactions were stronger than at 24 hours only 65 times in 1869 comparisons. One hundred forty-five (14.5 per cent) of the delayed reactions were large, red, warm, indurated areas 3 to 10 cm. in diameter. These were graded 4 plus. Small areas of central necrosis occurred in a few. Three hundred twenty-four (32.4 per cent) delayed reactions were 2-3 cm. in diameter, 2-3 plus. There were 535 (53.5 per cent) 1 plus delayed reactions, 1-2 cm. slightly indurated red areas; 0.025 ml. was the standard intracutaneous test dose.

Passive Transfer.—The passive transference of hypersensitivity to the skin of a nonallergic person, by intracutaneous inoculation with serum from an allergic person, is a cardinal test for the atopic or anaphylactic type of allergy. Passive transfer of skin reactivity to whole bacteria[20] and to the polysaccharide of *Bacillus abortus*[24] have been reported. Immediate wheal and flare, atopic-type skin reactions followed intracutaneous injections of polysaccharide and nucleoprotein fractions of bacteria in 21.5 per cent of 3860 tests. Confirmation of the atopic character of these reactions was attempted in 29 passive transfer tests with serum from 7 of the patients who had strong immediate reactions. Sera from 4 of these mediated 9 passive transfer reactions to 5 polysaccharide and 2 nucleoprotein bacterial fractions. Details of the immediate and passive transfer reactions are given in Table II. Control tests in unsensitized skin about 2 inches from the sensitized sites were all negative. Each of the passive transfer reactions exhibited typical flares with wheals and pseudopodia. Other attempts have not been made, because of the difficulty in finding recipients who do not react to bacterial fractions and be the statistical incidence of passively transferable skin hypersensitivity did not seem germane at present.

Analysis of 36 Patients Who Had Strong Skin Reactions.—Thirty-six cases were selected for detailed analysis, solely because they had strongly positive

skin reactions. Details of the analysis were tabulated. The resulting table had about 900 items in it. Table III contains an analysis of these items.

Twenty-six of these cases had strong immediate intracutaneous reactions. In ten the strong reactions were of the delayed type. Thirty-one of these patients had conventional allergy syndromes, such as hay fever, asthma, urticaria, angioneurotic edema, and atopic dermatitis. Three had rheumatoid arthritis. One had scleroderma. One was a diabetic with a large carbuncle and scars of hundreds of furuncles. In 19 of these cases infection was obvious in the sinuses, prostate, bronchi, tonsils, or pharynx. In 17 there was no evidence of infection. Intracutaneous reactions to inhalant atopens were strong in 17 cases. They were negligible in 16. They were not done in 3 others. Intracutaneous reactions to food atopens were strong in 18 cases. They were negligible in 15. They were not done in 3.

The organisms used were the same 14 listed in Table I. Eight vaccines and 24 different fractions were used: 16 polysaccharides and 8 nucleoproteins.

In the 36 selected cases there were 644 positive skin reactions, an average of 18 per patient; 320 were of the immediate, wheal and flare, atopic type; 324 were of the delayed type. In 3 cases there was a total of 13 immediate reactions of the cutaneous (scratch) type. There were 200 strong (2-4 plus) delayed as against 115 strong immediate intracutaneous reactions.

Eleven of the 24 fractions elicited 6 or more strong reactions. Each of the 36 patients had at least 4 positive reactions. Seven of them had 25 or more, while 32 had 10 or more positive reactions.

Two hundred eight of the 644 positive skin reactions were due to vaccines. The strength and incidence of delayed reactions to vaccines were appreciably greater than the immediate reactions. The number of immediate reactions to vaccines, 83, was surprising.

Individual intracutaneous reactions tended to be either immediate or delayed. In other words, most of the immediate reactions disappeared or faded markedly by the next day, whereas, most of the delayed reactions were preceded by negative or weak immediate reactions. There were numerous exceptions.

DISCUSSION

A large number of persons had a large number of immediate and delayed skin reactions to 34 arbitrarily selected bacterial fractions. The immediate and the delayed reactions were just as striking in patients without obvious infection or allergy as in those who had chronic pansinusitis, for example, or typical allergic syndromes with strong food and inhalant reactions. This is not surprising. Lifelong exposures to bacteria and their products in normal and diseased skin and respiratory, gastrointestinal, and genito-urinary systems could be expected to result in cutaneous sensitization as readily as the inhalation of dust, or the injection of insulin, liver extract, or heterologous serum. Thus, positive skin reactions may be due to immunological experiences entirely unrelated to the syndrome presented by the patient.

TABLE II. LOCAL PASSIVE TRANSFER OF HYPERSENSITIVITY TO POLYSACCHARIDE AND NUCLEOPROTEIN FRACTIONS OF BACTERIA

PATIENT	CLINICAL DIAGNOSIS	REACTIONS	AEROGEN CHO*(13)	PYOCYAN CHO(17)	B. HEMO STREP. CHO(19)	MICROCOCCUS CHO(24)	HEMO STAPH. AUREUS CHO(35)	HEMO STAPH. AUREUS NP†(43)	B. HEMO STREP. NP(47)
Hat	Asthma Hay fever	Immediate		3+		1+S		1+S	1+S
		Pass. transfer		1+		2+		1+	1+
Haw	Diabetes Carbuncles	Immediate	2+				4+		
		Pass. transfer	1+				1+		
Mene	Asthma	Immediate					3+		
		Pass. transfer					2+		
Stra	Chronic prostatitis Scleroderma Hypertrophic arthritis	Immediate	1+				3+		
		Pass. transfer	1+				1+		

*CHO = Polysaccharide.
†NP = Nucleoprotein.

TABLE III. SUMMARY OF DETAILED ANALYSIS OF 36 CASES WHO HAD STRONG REACTIONS TO 24 BACTERIAL FRACTIONS

Selection of Cases					
Strong immediate reactions to fractions					26
Strong delayed reactions to fractions					10
Total					36
Diagnoses					
Conventional allergy					31
Arthritis					3
Scleroderma					1
Diabetes with carbuncles					1
Total					36
Other Data					
Infection obvious					19
Infection not obvious					17
Total					36
Inhalant reactions:					
strong					17
negligible					16
not done					3
Total					36
Food reactions:					
strong					18
negligible					15
not done					3
Total					36
Number of organisms used for fractions (Staph. aureus and albus, Str. hemo. and viridans and fecalis, aerogenes, coli, influenza, pertussis, Friedländers, micrococcus, pyocyaneous, pneumo. Type I, subtilis)					14
Number of fractions used					
Polysaccharides					16
Nucleoproteins					8
Total					24
Number of vaccines used (Staph. aureus hemo, B. hemo strep., Str. fecalis, micrococcus, aerogenes, coli, pyocyaneous, Friedländers)					8
Analysis of skin reactions					
	Reaction	Fractions	Vaccines		
Immediate intracutaneous	1+	134	58		
	2-4+	90	25		
Cutaneous (3 cases)		13	0	320	
Delayed intracutaneous	1+	87	37		
	2-4+	112	88	324	
Total number of reactions (Av. = 18 per patient)				644	
Number of fractions eliciting 6 or more strong reactions					11
Polysaccharides				8	
(Strep. hemo (19), pyocyaneous (17), staph. aureus (35) and (10), aerogenes (13), micrococcus (24), strep. viridans (11), strep. fecalis (5))					
Nucleoproteins				3	
(Staph. albus (20) and (42), staph aureus (43)					
Smallest number of reactions per patient				4	
Number of patients with 25 or more reactions				7	
Number of patients with 10 or more reactions				32	

Positive cutaneous reactions do not differentiate preclinical, subclinical, clinical, or postclinical states. Nor do they, alone, ever determine the etiological importance of an antigen. The etiological significance of a positive skin reaction must be determined by clinical means.[23] Tests with bacterial fractions are subject to the same difficulties of clinical application as are those with food and inhalant extracts. The wheal and flare reactions and the passive transfer of hypersensitivity show that bacterial antigens can elicit atopic responses frequently.

The methods of preparation of the fractions used in this study yield crude products. The terms "polysaccharide" and "nucleoprotein" do not imply complete absence of protein from polysaccharide nor of polysaccharide from nucleoprotein, nor the absence of other antigens from either. In spite of these necessary reservations there were the striking tendencies for: (1) the polysaccharides to cause immediate reactions; (2) the nucleoproteins to cause delayed reactions; (3) the immediate to be followed by negative or weaker delayed reactions; (4) the delayed to follow negative or weaker immediate reactions. The exceptions require special study. Perhaps purer fractions would emphasize or refute these observations.

These tendencies are in line with the demonstrated capacity of the polysaccharide to produce a wheal and flare-anaphylactic response[13, 14] and of the nucleoprotein to cause the tuberculin-type of local reaction.[15-17]

These observations suggest that the immediate and delayed reactions may be different responses and not phases of the same reaction. More study is needed.

Delayed reactions present another problem. Most of them reached maximal intensity within 20 hours. There were 1869 48- and 24-hour readings. They were the same 1131 times. The 48-hour was weaker than the 24-hour reading 673 times. The 48-hour was stronger than the 24-hour reading only 65 times.

Delayed clinical focal responses to foods, inhalants, and to allergen injections are somewhat analogous to these delayed cutaneous reactions. Is the delayed reaction determined by the antigen, the state of the tissues, or both? Is it specific? Is it the Arthus, tuberculin, or other type of reaction? Evidence upon which to settle these important problems is not available.

SUMMARY

1. The results of 3860 intracutaneous tests with 34 crude polysaccharide and nucleoprotein fractions of 14 kinds of bacteria are analyzed.

2. It cannot be concluded that intracutaneous reactions to bacterial fractions have lessened the problems of the etiological diagnosis or treatment of bacterial allergy. Too many links are missing.

3. The data presented do show conclusively, however, that: crude, easily prepared, soluble polysaccharide and nucleoprotein fractions of a wide variety of bacteria elicit a high incidence of immediate wheal and flare reactions which are indistinguishable from those produced by extracts of foods and inhalants.

4. A high incidence of delayed reactions was observed, also. Most of the delayed reactions reached their maxima in about 20 hours. There are no data

which permit their classification as tuberculin, Arthus, or other delayed reactions.

5. The term "Bacterial allergy" should not be used to designate solely the delayed tuberculin-type of hypersensitivity. Bacterial allergy manifests itself, in the skin at least, in both immediate and delayed reactions.

6. Tests with purer bacterial fractions should emphasize or minimize the observed tendency for polysaccharides to elicit the immediate and for nucleoproteins to elicit delayed reactions.

7. Diagnostic procedures other than skin tests are needed to establish etiological relationships between bacteria and syndromes of clinical allergy.

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ELECTROCARDIOGRAPHIC STUDIES IN BRONCHIAL ASTHMA*

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MANY studies have been reported upon the relationship of cardiac changes to chronic bronchial asthma. Of these, a number have been based upon the interpretation of electrocardiograms. From these studies, some workers have concluded that "there is definite damage or tendency toward damage to the heart in bronchial asthma."[1] Others[2] have drawn a diametrically opposite conclusion and feel that the heart suffers very little damage in bronchial asthma. Thus, one of the earliest workers, Kahn,[3] reported that in 50 cases he found 10 cases of "right ventricular preponderance," 21 of "left ventricular preponderance," and 19 "normal" electrocardiograms. Colton and Ziskin[4] reported their electrocardiographic studies in 56 cases of whom 11 were reported as being abnormal. Harkavy and Romanoff[5] likewise reported that they interpreted 20 of their 50 cases as being abnormal. Schiller, Colmes, and Davis[6] reported electrocardiograms in 46 cases; of these they reported only 15 as within normal limits and 31 as abnormal. Urbach[7] reported that 62, or 29 per cent, of 209 cases had evidence of "myocardial involvement" during asthma-free intervals, implying probable permanent changes. The conclusions of most of these workers were based upon studies limited either to the three standard leads, or upon these leads plus one precordial lead, and axis deviation per se or minor changes were in many cases interpreted as direct evidence of myocardial involvement or damage.

The present study consists of 50 cases of bronchial asthma in whom electrocardiographic studies were made either during asthma-free intervals, or, in cases of chronic persistent bronchial asthma, during the period of minimal asthma. All electrocardiographic studies included the 3 standard leads, Wilson precordial Leads V_1 through V_6, and V_{3R}, and the augmented limb Leads aV_R, aV_L, and aV_F. Of the 50 cases, extrinsic allergic factors were found in 39, or 78 per cent, while the remainder were considered "intrinsic" or bacterial. The majority of the cases were in the older age groups, all being over 20, and 30 over 50 years of age. The duration of asthma is listed in Table I. As demonstrated, 34 of the cases were of over 6 years' duration, while 23 were of over 11 years' duration.

TABLE I. DURATION OF ASTHMA

Less than 1 year	2
1 to 5 years	14
6 to 10 years	11
11 to 15 years	3
16 to 20 years	7
21 to 30 years	9
Over 30 years	4

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The relationship of axis deviation to bronchial asthma and of axis deviation to position of the heart is analyzed in Table II.

TABLE II. RELATIONSHIP OF AXIS DEVIATION TO POSITION OF HEART

	HORIZONTAL	INTERMEDIATE	VERTICAL	TOTALS	
Neutral axis	0	4	28	32	
Right axis deviation	0	0	4	4	
Left axis deviation	7	5	1	13	
Totals	7	9	33	49	(One case of right bundle branch block not included)

Exclusive of axis deviation, which, in the majority of the cases studied was due to changes in the position of the heart, 9 patients were considered to have abnormal electrocardiograms and 41 were considered to be normal. The following is a brief review of the 9 patients considered to have abnormal electrocardiograms:

CASE REPORTS

CASE 1.—A 69-year-old white man had had whooping cough at age of 3, and recurrent asthmatic attacks since that time, usually in the winter. Hay fever, age of 21 to 40, also hives and eczema. Admitted to hospital several times in status asthmaticus. Extrinsic inhalant factor demonstrated. Patient also had hypertension and coronary heart disease. Examination revealed pulmonary emphysema in addition to asthmatic findings. X-ray studies revealed slight emphysema in upper lung fields; heart on physical examination, normal. Electrocardiograms revealed evidence of left and right ventricular myocardial damage (inverted T-waves in V_1, V_2, and V_3).

CASE 2.—A 54-year-old white man had had bronchial asthma in 1918, then recurrence in 1941, and asthma since that time. Also urticaria. Extrinsic inhalant factors demonstrated. He had also coronary heart disease, angina pectoris, and diabetes mellitus. Examination revealed pulmonary emphysema in addition to asthmatic findings. X-ray examination revealed moderate pulmonary emphysema and a narrow vertical heart. Electrocardiogram revealed right bundle branch block.

CASE 3.—A 60-year-old white man had had bronchial asthma of 30 years' duration, originally seasonal, then perennial for many years. Extrinsic inhalant factors demonstrated. Had also marked hypertension, blood pressure 200/120 on admission. Examination revealed moderate pulmonary emphysema. X-ray examination revealed moderate pulmonary emphysema at bases, moderate enlargement of heart in transverse diameter. Electrocardiogram showed left ventricular hypertrophy with strain.

CASE 4.—A 37-year-old white man had had asthmatic attacks since childhood, at first seasonal, then perennial for several years. Multiple extrinsic factors demonstrated. Two years prior to admission, history of dyspnea without much wheezing. Admitted to hospital on present occasion because of ankle edema. Had no asthma while in hospital. Examination revealed pulmonary emphysema; occasional expiratory wheeze heard. Heart normal in size; blood pressure normal. X-ray examination revealed lungs and heart normal. Electrocardiogram revealed left ventricular hypertrophy with myocardial damage; these changes reverted to normal, however, before patient was discharged from hospital.

CASE 5.—A 51-year-old white man had had asthma of 4 years' duration, continuous for 10 months. Extrinsic inhalant factors demonstrated. Examination revealed patient markedly orthopneic, chest markedly emphysematous with almost total absence of breath sounds. X-ray examination revealed marked pulmonary emphysema, heart narrow vertical type. Electrocardiogram revealed left axis deviation, vertical heart, low voltage probably due to severe pulmonary emphysema; low T-waves suggesting myocardial damage on July 9, 1948. On Aug. 2, 1948, revealed evidence of impure auricular flutter. On Aug. 9, 1948, normal rhythm, but other findings unchanged.

CASE 6.—A 56-year-old white man had had hay fever from age 26 to 49; then asthma, at first seasonal, later perennial. Extrinsic inhalant factors demonstrated. Examination revealed slight emphysema in addition to asthmatic findings. X-ray examination revealed slight pulmonary emphysema, some evidence suggestive of concentric hypertrophy of left ventricle. Electrocardiogram showed neutral axis, vertical heart, diphasic T-waves in V_5 and V_6.

CASE 7.—A 52-year-old white man had had asthma since age of 8, severe at first, then relatively mild until 1946, severe and perennial since that time. Multiple extrinsic factors demonstrated. At time of admission, he had marked peripheral edema, hepatomegaly in addition to dyspnea, and was diagnosed cor pulmonale. Examination revealed limited expansion of chest and typical asthmatic findings. X-ray examination showed no pulmonary emphysema and no cardiac enlargement. Electrocardiogram at time of admission revealed findings interpreted as due to right ventricular hypertrophy with strain. V_{3R} showed deep Q measuring 6 mv., but R measured 10 mv. Possibility of subepicardial infarction was also considered. Electrocardiogram reverted to within almost normal limits during period of observation (Fig. 1).

CASE 8.—A 53-year-old white man, with chronic productive cough, associated with wheezing since age of 33; frank asthmatic attacks during two years prior to admission. Pneumonia on three occasions. No extrinsic allergic factors demonstrated. Admitted with marked dyspnea, cyanosis, hepatomegaly, and peripheral edema, and diagnosed cor pulmonale. Examination revealed evidence of marked pulmonary emphysema in addition to asthmatic findings. X-ray examination revealed marked pulmonary emphysema, heart narrow, vertical type. Electrocardiogram on admission showed changes interpreted as right ventricular hypertrophy with strain. Electrocardiogram reverted to normal during period of observation (Fig. 2).

CASE 9.—A 39-year-old Negro woman had had asthma of 30 years' duration with numerous admissions for status asthmaticus. Extrinsic allergic factors demonstrated. Examination indicated moderate pulmonary emphysema. X-ray examination revealed only evidence of increased bronchial markings. Patient showed abnormally enlarged P waves in Leads II and III (P-pulmonale) at time of admission for status asthmaticus on present occasion, which returned to normal after her status asthmaticus improved.

Summary of the above-described abnormal electrocardiograms and their relationship to the patients' asthma is shown in Table III.

TABLE III. SUMMARY OF ABNORMAL ELECTROCARDIOGRAMS

PROBABLY UNRELATED to asthma:	4
(Cases 1, 2, 3, and 4)	
Myocardial damage, cause undetermined	1
Associated with hypertension and coronary arteriosclerosis	3
POSSIBLY RELATED to asthma:	3
(Cases 4, 5, and 6)	
T-wave changes in precordial leads	3
PROBABLY RELATED to asthma:	3
(Cases 7, 8, and 9)	
"Right ventricular hypertrophy" with damage	2
Transient P-pulmonale	1

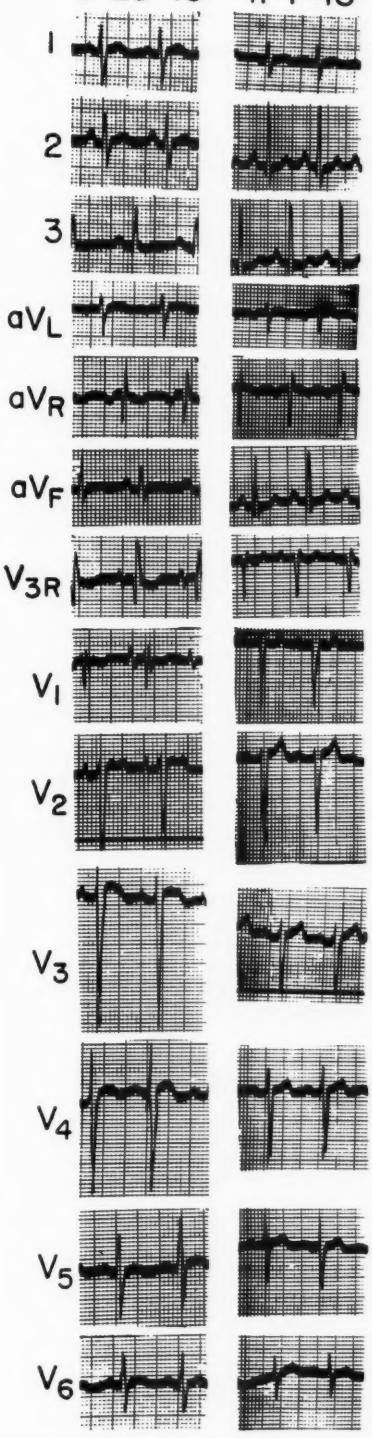

Fig. 1.

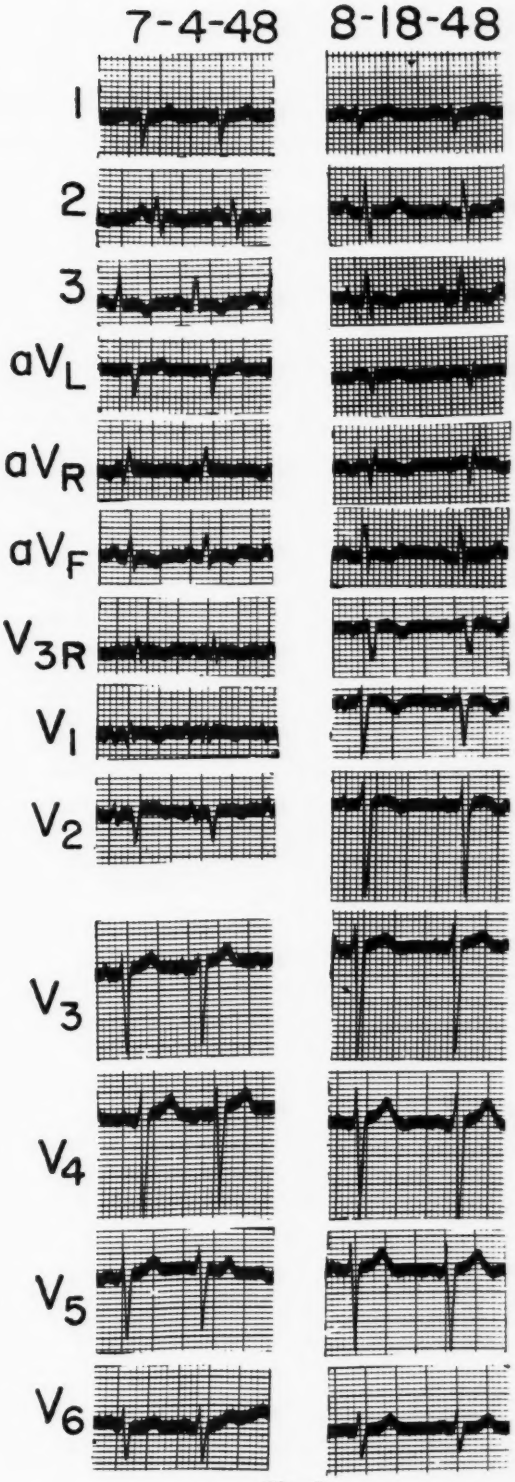

Fig. 2.

Fig. 1.—(Case 7) On May 28, 1948, shortly after admission with cor pulmonale, R in aV_R and V_{3R} were very large. On Nov. 1, 1948, R in aV_R had become much smaller and R in V_{3R} very small.

Fig. 2.—(Case 8) On July 4, 1948, shortly after admission with cor pulmonale, there was definite right axis deviation, definitely enlarged R in V_{3R}. On Aug. 18, 1948, after treatment, axis deviation was minimal, and R in V_{3R} had almost completely disappeared.

DISCUSSION

Evaluation of electrocardiographic changes in bronchial asthma must give due consideration to alterations due to position of the heart as well as to other conditions coexistent which may be productive of cardiac pathology. Study of axis deviation in this series revealed that most of the changes were due to change in the position of the heart. There was right axis deviation in 5 cases, left axis deviation in 13, and no axis deviation in the remaining 32. Analysis of the relationship of position of the heart determined by changes in the unipolar limb and precordial leads revealed that 34, or 68 per cent, had vertical or semivertical position of the heart. This is, of course, compatible with changes occurring with pulmonary emphysema and associated flattening of the diaphragms. It is interesting to note that while the majority of the cases of left axis deviation were associated with horizontal or semihorizontal position of the heart, and of the cases of right axis deviation with vertical or semivertical position of the heart, 28 of the 32 cases of "neutral axis" or with no deviation, had vertical or semivertical position. Of the 3 cases with abnormal electrocardiograms considered as possibly due to asthma, one had neutral axis and 2 had left axis deviation. Of the 2 cases of "right ventricular hypertrophy" considered probably due to asthma, one had neutral axis, and the other right axis deviation, which later became neutral. It is thus seen that interpretation of an electrocardiogram as revealing myocardial involvement on the basis of axis deviation alone is unwarranted.

In the present series of cases, only 6, or 12 per cent, were considered as possibly or probably due to the bronchial asthma. Of the cases probably due to asthma, one had enlarged P waves, of P-pulmonale, which was transient and not associated with other electrocardiographic changes. The other 2, which are quite interesting (Figs. 1 and 2), had changes in the early electrocardiograms compatible with a diagnosis of right ventricular hypertrophy with strain and compatible with their clinical picture of cor pulmonale. In both of these cases, however, the electrocardiograms had reverted to normal or almost normal during the period of observation, and could not, therefore, have been actually due to muscular hypertrophy. Thus, it is seen that of the 3 cases in whom electrocardiographic abnormalities were interpreted as being due to the asthma, none had permanent changes. Of the other 3 cases interpreted as possibly due to asthma, the changes which consisted of altered T-waves in the precordial leads, one had hypertension also to which the T-wave changes might have been due. Thus, it is felt that permanent myocardial changes due to bronchial asthma, as revealed by electrocardiographic studies, are uncommon.

SUMMARY

1. Fifty cases of bronchial asthma were studied electrocardiographically with standard leads, multiple precordial leads, and augmented limb leads.

2. Only 3, or 6 per cent, were interpreted as having electrocardiographic abnormalities probably due to asthma, and the changes in these were transient. Three others were interpreted as being possibly due to asthma. Forty-four, or

88 per cent, revealed no changes which could be interpreted as revealing myocardial hypertrophy or damage due to asthma.

3. Significant persistent electrocardiographic changes due to bronchial asthma are uncommon.

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ANTIHISTAMINIC EFFECTS OF N,N-DIMETHYL-N′-(3-THENYL)-N′-(2-PYRIDYL)-ETHYLENEDIAMINE (THENFADIL) APPLIED TOPICALLY*

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SINCE the discovery of the antihistaminic activity in synthetic drugs, attempts have been made to antagonize the effects of histamine on the human skin. Staub[1] found that previous or simultaneous administration of N-phenyl-N-ethyl-N′,N′-diethyl-ethylenediamine (1571F) by iontophoresis failed to antagonize the effect of histamine similarly applied. Sciclounoff and Junet[2] and Parrot[3] were able to demonstrate a decrease in the erythema and whealing induced by histamine applied by puncture to the skin after oral administration of N′-phenyl-N′-benzyl-N,N-dimethyl-ethylenediamine (Antergan) a more potent antihistaminic drug.

Feinberg and Friedlaender[4] found that beta-dimethylaminoethyl benzohydryl ether hydrochloride (diphenhydramine)† given by mouth was effective in urticaria factitia and in reducing or inhibiting dermographism, two conditions in which a local release of histamine appears to play an important part.[5, 6] Baer and Sulzberger[7] obtained fair to excellent relief of the urticaria in a majority of a small group of patients by the daily oral administration of 50 to 300 mg. of tripelennamine.‡ In a case of dermographism, 150 mg. of tripelennamine, given orally, greatly reduced, but did not abolish, the urticarial response to a standard stimulus applied 50 minutes later.[8]

Later Friedlaender and Feinberg[9] tested diphenhydramine against histamine and observed that oral doses of 50 mg. had very little effect on the skin reactions to histamine applied one hour later by the scratch technique in serial dilutions from 1:1000 to 1:32,000. They found, however, that the wheals on the control side were larger than those obtained by similar solutions of histamine which either contained 5 per cent diphenhydramine or were applied on scratches already treated with 5 per cent diphenhydramine. All these tests were carried out on ragweed-sensitive patients along with parallel tests with serial dilutions of ragweed extracts. In all the tests, diphenhydramine affected histamine and ragweed antigen-antibody skin reactions to approximately the same degree. Somewhat different results were obtained by Cohen and co-workers.[10] They found that diphenhydramine, given orally, increased the histamine threshold of the skin as determined by the administration of serial dilutions by iontophoresis.

Other investigators have found the following drugs orally effective in reducing the skin reactions to histamine locally applied: diphenhydramine,[11] Antergan,[11] N,N-dimethyl-N′-(2-pyridyl)-N′-(p-methoxybenzyl)-ethylenediam-

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†Benadryl is the registered trade-mark of Parke, Davis & Company, Detroit, Mich., for diphenhyramine.

‡Pribenzamine is the registered trade-mark of Ciba Pharmaceutical Products, Inc., for tripelennamine.

ine (Pyranisamine),*[11] 2-(N-benzyl-N-phenyl-aminomethyl)-imidazoline hydrochloride (phenazoline),† N,N-dimethyl-N′-(2-pyridyl)-N′-benzyl-ethylenediamine (tripelennamine),[12] N,N-dimethyl-N′-(2-pyrimidyl)-N-(p-methoxybenzyl)-ethylenediamine (thonzylamine),‡[13] 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (Thephorin).[14]

Recently the antihistaminic activity of three new compounds, i.e., N′-(2-pyridyl)-N′-(3-thenyl)-N,N-dimethylethylenediamine (Thenfadil§), the 2-chlorothenyl (WIN 2875) and the 2-bromothenyl (WIN 2876) analogs, synthesized by Campaigne and Le Seur,[15] has been investigated in this laboratory.[16] Thenfadil was found to be more effective than the other two compounds in antagonizing histamine on the isolated guinea pig uterus and bronchioles. Parallel tests run with the 2-thenyl analog (thenylpyramine) showed that 3-thenyl substitution increased the antihistaminic activity.

In toxicity tests in guinea pigs, 1 micromol of Thenfadil neutralized the effect of somewhat more than 50 micromols of histamine base.

On the basis of these findings, it was decided to determine the degree of protection afforded by Thenfadil against the local effect of histamine in man when both drugs were applied directly to the skin.

In order to approximate the conditions under which the antihistaminic drugs might be used locally in clinical cases the method of application chosen was one in which both histamine and the antihistaminic drugs were absorbed through the intact skin.

The effectiveness of some surface-active agents in promoting percutaneous absorption has been demonstrated by Duemling[17] and Herrmann, Sulzberger, and Baer[18] and later by others. This was confirmed by extensive comparative studies on the influence of different vehicles on the skin penetration of various tracer substances (MacKee, Sulzberger, Herrmann, and Baer[19]). In these studies the most probable route of maximum penetration was also determined.

Penetration of histamine[20, 21] and epinephrine[20] through the intact skin has been demonstrated in man and rabbits when these substances, dissolved in vehicles containing sodium alkyl benzene sulfonates, were applied by inunction.

Investigations in which one of us participated[22] have shown that vehicles containing octyl alcohol are very effective in promoting the skin absorption of epinephrine and acetyl-beta-methyl-choline (Mecholyl) in rabbits. Based on the results obtained in rabbits, a mixture containing octyl alcohol (technical), diethyl-eneglycol monoethyl ether, ethyl alcohol, and water was used as a vehicle for histamine and the antihistaminics in most of the experiments described here.

EXPERIMENTAL DATA

All the experiments were carried out on 23 volunteers. The vehicle (hereafter termed "C.O.W.E. mixture") for histamine dihydrochloride and for the

*Neo-Antergan is the registered trade-mark of Merck and Company, Inc., Rahway, N. Y., for Pyranisamine.

†Antistine is the registered trade-mark of Ciba Pharmaceutical Products, Inc., Summit, N. J., for phenazoline.

‡Neohetramine is the registered trade-mark of Wyeth, Inc., for thonzylamine.

§Trade-mark, Winthrop-Stearns, Inc.

antihistaminic drugs contained the following substances:

Diethylene glycol monoethyl ether (Carbitol)	5 c.c.
Octyl alcohol (technical)	3 c.c.
Distilled water	2 c.c.
Ethyl alcohol	0.36 c.c.

A mixture of equal parts of carbitol and octyl alcohol containing 10 per cent of water has been found to be the most convenient vehicle for epinephrine and Mecholyl as it is noninjurious and very active in promoting the absorption of these drugs.[22] A smaller proportion of octyl alcohol in the mixture also resulted in good absorption. Ethyl alcohol was used originally to facilitate the solution of some of the drugs used,[22] but perhaps it could have been omitted. The solvent mixture had no visible effect on the skin; repeated application on the same areas of the forearm was well tolerated. In all the subjects the skin appeared completely normal at the end of the two series of experiments.

No attempt was made to determine the effect of changes in the formula on the degree of absorption of histamine and the antihistaminics once it had been demonstrated that these drugs were absorbed, with the exception of a few experiments in which histamine was dissolved in water or in Carbitol alone. Histamine in Carbitol appeared to be less effective than in the solvent mixture containing octyl alcohol. A one per cent concentration of histamine in water had no effect in one individual; in another a 5 per cent solution had less effect than a 1 per cent solution in the solvent mixture described above. In these experiments, carried out in February, the solutions were rubbed on the skin. However, in July, a solution of 2 per cent of histamine dihydrochloride (in terms of the base) in distilled water, applied without rubbing, produced a strong reaction in the same individuals. Differences in skin temperature may account for the lesser reaction obtained in the winter. These results are in agreement with the findings of Shelley and Melton[23] who demonstrated absorption of histamine both as the free base and the diphosphate, through human skin from aqueous solutions.

Two series of experiments were carried out, differing somewhat in the technique used. In both series, histamine dihydrochloride and the antihistaminic drugs were dissolved in the C.O.W.E. mixture. The concentration of histamine was expressed in terms of the base and that of the antihistaminics in terms of their salts.

Series A.—In this series, two drops of one per cent histamine solution were applied to an area of the subject's forearm outlined by a 9 sq. cm. hole in a curved aluminum plate. The solution was gently rubbed over the skin for 3 minutes with the bottom of a test tube. The plate was used to circumscribe the area of application but it was found that the solution tended to creep so that the area exposed was somewhat larger (16 sq. cm.) than the opening. Allowance was made for this in applying the antihistaminic prior to the histamine by using a plate with a slightly larger hole.

One of the disadvantages of this method of application resulted from the pressure applied in rubbing, thereby influencing the degree of absorption, a factor which was difficult to keep constant, although all the tests were run by the same observer. To obviate this, a new method of application was devised.

Series B.—Four drops of a solution of histamine (2 per cent) were applied and spread gently, without further manipulation, in an area of about 15 square centimeters. The plate was not used.

The effect of histamine was essentially the same in both series of tests, although the first method of application was more effective, as the one per cent solution gave approximately the same readings as the 2 per cent solution in Series B.

In order of appearance, the first symptom observed was pruritus, which began one to two minutes after beginning the application. It was more intense in the second series in which the skin was not rubbed. Redness next appeared and finally wheals. The itching disappeared in a few minutes and the other symptoms gradually thereafter.

The wheals were usually numerous, punctiform at the beginning and gradually increasing in size. A scoring system (Table I) was devised to estimate the effect of histamine. The scoring of the erythema was based on the size of the flare, the degree of redness, and whether it was uniform or splotched. The degree of whealing was gauged by the number and size of recognizable wheals (more than one mm. in diameter).

TABLE I. SCORING SYSTEM OF HISTAMINE SKIN EFFECTS

PRURITIS		ERYTHEMA		WHEALS		
				SIZE (DIAMETER)	NUMBER	
Intense	4	Intense flare	4	More than 1 mm.	More than 25	4
Marked	3	Moderate	3	More than 1 mm.	15 to 25	3
Mild	2	Mild	2	More than 1 mm.	Less than 15	2
Barely perceptible	1	Only red spots	1	Only minute or flat		1
Absent	0	Absent	0	Absent		0

Maximum value: $12 = 4(P) + 4(E) + 4(W)$

For the purpose of scoring, the presence of small red or purple spots, undoubtedly produced by the direct action of histamine, is included under "erythema," together with the flare, which has previously been shown to be due to an axon reflex. In a well-developed histamine reaction obtained through the intact skin, no purplish spots are observed, since the local vasodilation is masked by the concomitant development of the wheals. The vascular effect can be seen only where whealing is prevented by the antihistaminics. In this sense, each red spot marks the site where a wheal failed to develop. In the histamine-antihistaminic drug ratio used, the direct vascular action of histamine was never abolished and therefore the presence of the "red spots" was the minimum degree of erythema that could be observed under the influence of the antihistaminics.

The scoring of the itching was not difficult when it was very intense or absent. The intermediate values were, of course, only approximate and reflected differences in degree of itching which the subject was able to perceive between the two areas of application.

The average score for histamine alone at a concentration of one per cent in Series A was between 10 and 11 and for the 2 per cent in Series B was 11 with a range of 8 to 12 in the group selected to carry on the planned tests. Subjects

with scores of 7 or lower were rejected; these low scores occurred in the majority of the men tested, while scores of 8 or higher occurred in the majority of the women. Consequently, the group of subjects selected for testing the antihistaminics included a very small proportion of men.

In estimating the antihistaminic effect, the values given in the tables under the heading of "Degree of Protection" represent the difference observed between the histamine reaction before and after (or with) the antihistaminic drug. In other words the degree of protection is the value obtained by subtracting the histamine reading after (or with) the antihistaminic drug from the control reading.

Drugs Used.—Histamine dihydrochloride, Thenfadil, tripelennamine hydrochloride,* thenylpyramine hydrochloride,† and diphenhydramine hydrochloride.

RESULTS

Series A.—In the first group of experiments histamine one per cent and the antihistaminic drug, either Thenfadil or tripelennamine, were applied in the same solution. Results are summarized in Table II.

TABLE II. POTENCIES OF THENFADIL AND TRIPELENNAMINE IN REDUCING THE EFFECTS OF HISTAMINE
(Histamine 1 per cent and antihistaminic applied in the same solution)

ANTI-HISTAMINIC	CONCENTRATION‡ (%)	SUBJECTS TESTED	NUMBER OF TESTS	AVERAGE HISTAMINE CONTROL READING	AVERAGE EXPTL. READING	NUMERICAL DIFFERENCE	DEGREE OF REDUCTION (%)
Thenfadil	10	5	5*	11	3.0	8.0	73
Tripelennamine	10	5	5*	11	4.2	6.8	63
Thenfadil	5	9	10†	10.6	3.6	7.0	66
Tripelennamine	5	8	10†	10	5.0	5.0	50

*Only one of the five values was obtained in parallel tests.
†Eight out of ten were obtained in parallel tests.
‡In terms of the hydrochlorides.

As indicated in Table II, both Thenfadil and tripelennamine are very effective in counteracting the effect of histamine when applied in the same solution, Thenfadil being somewhat more effective.

In another group of experiments a one per cent solution of histamine was applied to areas already treated with the antihistaminics. In each group of tests, the antihistaminics were applied simultaneously on comparable areas of the two forearms (Table III).

A fairly good degree of protection was obtained with Thenfadil, tripelennamine, and thenylpyramine. Benadryl was least effective. Again the highest values were obtained with Thenfadil at the various concentrations used with the exception of one group of experiments which included only two tests. The effects of Thenfadil and of tripelennamine were still distinct 5 hours after application.

*Courtesy of Dr. F. F. Yonkman, Ciba Pharmaceutical Products, Inc.
†Courtesy of Dr. K. K. Chen, Eli Lilly & Co. (Histadyl is the registered trade-mark of Eli Lilly and Co. for thenylpyramine.)

TABLE III. HISTAMINE ONE PER CENT APPLIED AFTER THE ANTIHISTAMINICS

GROUP OF EXP. (NO.)	COMPOUND	CONCENTRATION* (%)	TIME OF APPLICATION BEFORE HISTAMINE (HOURS)	NUMBER OF SUBJECTS TESTED	NUMBER OF TESTS	AVERAGE CONTROL READING	AVERAGE EXPTL. READING	NUMERICAL DIFFERENCE (SCORE)	DEGREE OF REDUCTION (%)
1†	Thenfadil	5	1/6 - 1/3	4	5	10.4	2.6	7.8	75
2	Thenfadil	5	1	10	10	10.2	1.9	8.3	81
	Tripelennamine	5	1				3.0	7.2	70
3	Thenfadil	2	1	3	3	9.3	3.3	6.0	64
	Tripelennamine	2	1				4.0	5.3	57
4	Thenfadil	1	1	2	2	10.0	5.5	4.5	45
	Tripelennamine	1	1				5.0	5.0	50
5	Thenfadil	2	1	9	9	10.7	3.0	7 7	72
	Diphenhydramine	2	1				6.8	3.9	37
6	Thenfadil	1	1	7	7	10.0	2.6	7.4	74
	Thenylpyrnamine	1	1				4.6	5.4	54
7	Thenfadil	5	3	3	3	10.6	3.0	7.6	72
	Tripelennamine	5	3				6.6	4.0	37
8	Thenfadil	5	5	13	24	10.3	2.8	7.5	72
							3.9	6.4	62

*In terms of the hydrochlorides.
†Thenfadil was run against a histamine control. In all the other groups Thenfadil was applied on one arm and the other antihistaminic on the opposite arm.

Series B.—The antihistaminic drugs were dissolved in the solvent mixture (C.O.W.E.) and 6 drops were applied without rubbing one hour before histamine (4 drops of the 2 per cent solution in C.O.W.E. mixture on the area treated with the antihistaminic). All the tests were carried out on 14 volunteers. The results are summarized in Table IV. Although the method of application was somewhat different, the results are comparable to those obtained in Series A. Here again the over-all score obtained with Thenfadil was the highest, although in parallel tests with tripelennamine the difference in the scores was not significant. The antihistaminic potency of Thenfadil is more evident when the results shown in Table IV are tabulated on the basis of the percentage of the tests showing complete, partial, or no relief from the three main symptoms that characterize the histamine skin reaction. A summary of the results appears in Table V. The results show that the application of the 2 per cent histamine solution on the skin area treated one hour previously with a 5 per cent solution of Thenfadil produced absolutely no itching, flare, or wheals in 50 per cent of the tests, and no relief at all was reported in less than 20 per cent of tests. In this type of analysis of antihistaminic activity, Thenfadil again showed the highest potency. However, the numerical differences in the percentages obtained with the various antihistaminic drugs may not in all cases represent their relative potencies inasmuch as the values given in Table V are the sum of all the tests run with each drug. In comparing the effects of two drugs, values obtained in parallel tests are of greater significance.

TABLE IV. HISTAMINE TWO PER CENT APPLIED ONE HOUR AFTER THE ANTIHISTAMINICS
(Average histamine control reading = 11)

GROUP OF EXP. (NO.)	COMPOUNDS		CONCENTRATION* (%)	NO. OF SUBJECTS	NO. OF TESTS	AVERAGE EXPTL. READING	DEGREE OF REDUCTION		RELATIVE POTENCY IN INDIVIDUAL TESTS (NUMBER)		
							SCORE MEAN + S.E.	PER CENT	(I) AND (II) EQUAL. EFFECT	(I) MORE EFFECT	(II) MORE EFFECT
1	Thenfadil	(I)	2.5	12	12	5.5	5.5 ± 0.9	50	2	-	10
	Thenfadil	(II)	5.0			3.0	8.0 ± 0.6	70			
2	Thenfadil	(I)	5.0	14	28	4.2	6.8 ± 0.5	62	10	13	5
	Tripelennamine	(II)	5.0			5.2	5.8 ± 0.5	53			
3	Thenfadil	(I)	5.0	14	14	3.6	7.4 ± 0.7	67	-	12	2
	Diphenhydramine	(II)	5.0			7.6	3.4 ± 0.6	30			
4	Thenfadil	(I)	5.0	7	7	2.3	8.7 ± 0.7	79	1	5	1
	Thenylpyramine	(II)	5.0			5.3	5.7 ± 1.3	52			
5	Thenfadil	(I)	2.5	11	11	5.8	5.2 ± 0.9	47	3	5	3
	Thenylpyramine	(II)	5.0			5.6	5.4 ± 1.1	49			
6	Tripelennamine	(I)	5.0	10	10	5.0	6.0 ± 1.0	54	2	4	4
	Thenylpyramine	(II)	5.0			5.0	6.0 ± 1.0	54			

*In terms of the hydrochlorides.

TABLE V. RELIEF OF SYMPTOMS IN PERCENTAGE OF TESTS

COMPOUND	(%)*	NO. OF TESTS	PRURITUS			FLARE†			WHEALS		
			COMPLETE	PARTIAL	NONE	COMPLETE	PARTIAL	NONE	COMPLETE	PARTIAL	NONE
Thenfadil	5	61	52	29	19	48	40	12	51	44	5
Thenfadil	2.5	23	26	39	35	26	39	35	17	61	22
Diphenhydramine	5	15	0	21	79	7	64	29	0	36	64
Thenylpyramine	5	28	18	43	39	43	14	43	32	43	25
Tripelennamine	5	38	24	50	26	21	50	29	42	45	13

*In terms of the hydrochlorides.

†Only the effect on the flare is included in this column and therefore in the absence of flare, relief was considered complete even when punctiform vasodilation was present.

DISCUSSION

The experimental data presented here show that histamine and antihistaminic drugs produce their typical pharmacological action on the intact human skin when applied in the manner described. The degree of effect produced by a one or two per cent solution of histamine was fairly consistent on the same subject. By comparison with other methods of application reported in the literature (puncture, scratches, or iontophoresis),[4, 5, 10] it is evident that only a small proportion of the histamine applied in the C.O.W.E. mixture is absorbed. However, for the purpose of determining antihistaminic activity, the percentage absorbed is not very important as long as the histamine skin reactions are consistent.

In spite of the errors involved in the method of evaluating the skin reactions the estimation of antihistaminic potency gave fairly consistent results, especially in Series B in which results were obtained from a larger number of parallel tests for each group. These results show that a potent antihistaminic effect, especially for Thenfadil, was obtained. Histamine/antihistaminic ratios of 1:2.5, 1:1.25, or even 1:1 were obtained in some of the experiments in Series A. In Friedlaender and Feinberg's experiments the strongest solution of histamine used was 1:1000 against a concentration of the antihistaminic (diphenhydramine) of 5 per cent, that is, a ratio of 1:50.

Differences in absorption may have played a part in the degree of antihistaminic activity recorded. However, in the absence of experimental evidence indicating the amount of the drugs absorbed, it may be assumed that the main effect is due to inherent antihistaminic activity, as the relative potencies found are similar to those obtained in other laboratory tests in animals.[16]

The data in Table V show that the histamine itching, flare, and whealing can be inhibited in approximately the same proportion of tests. Two of these symptoms, the itching and the flare, result from either the direct or indirect action of histamine on the nerve endings (or fibers). Of the two symptoms that depend on the direct vascular action of histamine, only the increase in capillary permeability which results in whealing is affected by the antihistaminic; the direct local vasodilation (revealed by presence of red or purple spots) is not inhibited by any of the antihistaminics in the concentrations used.

Inasmuch as two of the symptoms produced by histamine are mediated by local sensory nerve fibers, the possibility that this particular aspect of the antagonism is related to the local anesthetic action which appears to be present in

most drugs of this type[24, 25, 26] must be considered. Although no local anesthetic action could be observed after the application of the antihistaminics in our experiments, the possibility of a slight action limited to a very small area around the point of penetration* and not detectable by the usual methods could not be excluded. To test this assumption a 5 per cent solution of Pontocaine in the C.O.W.E. mixture was applied to the skin of several subjects one hour before or simultaneously in the same solution with histamine. No local anesthetic effect was observed indicating that the absorbed drug never reached the threshold concentration for local anesthetic action as determined by pricking. There was evidence of slight antihistaminic action in only a few of the tests run. These results are in agreement with those obtained by Leavitt and Code[25] in parallel tests with diphenhydramine and procaine.

SUMMARY

1. Histamine dihydrochloride in one or two per cent solution (in terms of the base) in a mixture of diethylene glycol monoethyl ether, octyl alcohol, water and ethyl alcohol applied to the intact skin of human beings is rapidly absorbed and produces a typical local reaction in most of the subjects tested.

2. Various antihistaminic drugs dissolved in this vehicle, in concentration of one to 5 per cent and applied together with or before histamine on the same skin areas, reduced the histamine response.

3. A new antihistaminic, Thenfadil (N,N-dimethyl-N′-(3-thenyl)-N′-(2-pyridyl)-ethylenediamine), appears to be the most active of those tried in relieving the histamine skin symptoms.

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*Penetration probably takes place through the skin appendages as suggested by Rothman[27] and MacKee and co-worker.[19]

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CLINICAL STUDIES WITH IRON AS ADJUNCT TO POLLEN IMMUNIZATION AND ANTIHISTAMINIC THERAPY IN HAY FEVER*

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NUMEROUS publications have appeared during the past few years on the therapeutic effectiveness of antihistaminic substances for the treatment of various allergic conditions.[1] The antihistaminics have the characteristic competitive effect of displacing or replacing histamine, which is supposed to be the common denominator for many important allergic manifestations. Several useful antihistaminic compounds have been developed, most of which are chemically related to the phenolic ethers and derivatives of ethylenediamine. These compounds produce similar results in allergic patients and differ only in the degree of symptomatic relief obtained, side effects, and dosage.

Stavraky[2] noted that in decerebrated vagotomized cats, ferrous sulfate increased the effectiveness of small doses of Antistine in counteracting blood pressure changes induced by histamine, while calcium and potassium were ineffectual. He also administered ferrous sulfate orally to patients with seasonal hay fever or asthma in addition to antihistaminics such as Pyribenzamine or Antistine. He reported that the allergic manifestations were most effectively alleviated. The iron also seemed to relieve the lassitude and drowsiness induced by the antihistaminic agents. These observations encouraged further studies with the antihistamine-iron therapy in allergic individuals.

A study was made of all patients in our allergy clinic who were receiving pollen therapy for ragweed hay fever. We employed the antihistaminic Trimeton (prophenpyridamine)† which has been shown to be a useful drug for the relief of hay fever symptoms alone or in conjunction with standard pollen therapy.[3, 4] The iron preparation used was ferrous sulfate (enseal-coated) in order to minimize gastrointestinal disturbances, so common with iron medication. All patients received the regular immunization treatment with ragweed extract and were divided into 4 groups. From August 10th, to September 10th, Group 1 was given weekly supplies of 25 mg. Trimeton tablets and 5-gr. ferrous sulfate tablets. Group 2 was given Trimeton tablets and (as a placebo), sugar tablets similar in appearance to the iron tablets. Group 3 was given the iron and sugar tablets, while Group 4 received only the sugar tablets. Groups 1, 2, and 3 were instructed to take one tablet of each drug 3 times a day after meals, while those in Group 4 were instructed to take only the placebo. All patients were taught how to record their daily symptoms, impressions, and reactions, resulting from the use of any of the medications.

The hemoglobin of all patients was determined before and after completion of therapy, so that any marked improvement on iron therapy could be properly evaluated.

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†Trimeton was supplied through the courtesy of Schering Corporation, Bloomfield, N. J.

Hemoglobin was determined according to the method of King and his coworkers[5, 6] as modified by Horecker.[7] Blood samples were converted to alkaline hematin at a dilution of 1:251. The hemoglobin was determined in a photoelectric colorimeter using pure crystalline hemin as the standard.

Only those patients were included in this series of 150, upon whom complete treatment was possible and from whom proper records were available.

There is no practical objective method of measuring the degree of improvement following treatment for hay fever. We are, therefore, forced to rely upon the observer's evaluation of the subjective information obtained from the daily reports furnished by the patient and the over-all impression at the termination of the hay fever season.

The results following treatment were classified as complete or partial relief, or none. The patients with complete relief were those who had complete or almost complete freedom from hay fever symptoms. Those with partial relief has some noticeable hay fever symptoms, or at least 50 per cent relief, but which

TABLE I. RESULTS OF TREATMENT IN 150 HAY FEVER PATIENTS*

GROUP I: POLLEN THERAPY WITH TRIMETON AND IRON
Relief of Symptoms

Number of Patients	Complete	Partial	None	Total Relief
34	18 (53.0%)	8 (23.5%)	8 (23.5%)	26 (76.5%)

GROUP II: POLLEN THERAPY WITH TRIMETON ONLY
Relief of Symptoms

Number of Patients	Complete	Partial	None	Total Relief
60	39 (65.0%)	10 (16.7%)	11 (18.3%)	49 (81.7%)

GROUP III: POLLEN THERAPY WITH IRON AND PLACEBO
Relief of Symptoms

Number of Patients	Complete	Partial	None	Total Relief
28	16 (57.2%)	4 (14.3%)	8 (28.5%)	20 (71.5%)

GROUP IV: POLLEN THERAPY WITH PLACEBO ONLY
Relief of Symptoms

Number of Patients	Complete	Partial	None	Total Relief
28	16 (57.2%)	5 (17.8%)	7 (25.0%)	21 (75.0%)

*All patients received the standard immunization treatment with pollen extracts.

TABLE II. RESULTS WITH POLLEN THERAPY

GROUPS I-II: POLLEN THERAPY WITH TRIMETON
Relief of Symptoms

Number of Patients	Complete	Partial	None	Total Relief
94	57 (60.6%)	18 (19.2%)	19 (20.2%)	75 (79.8%)

GROUPS III-IV: POLLEN THERAPY WITHOUT TRIMETON
Relief of Symptoms

Number of Patients	Complete	Partial	None	Total Relief
56	32 (57.1%)	9 (16.0%)	15 (26.8%)	41 (73.2%)

caused them little suffering or inconvenience. Those classified as none had no relief whatsoever.

A comparison of the results obtained by the 4 groups (Table I) indicates that iron does not augment the therapeutic effect of specific immunization therapy, nor does it enhance the action of the antihistaminic, Trimeton. While immunization treatment with specific pollen extracts is the most effective single procedure for hay fever, greater relief is afforded when a potent antihistaminic, such as Trimeton, is used in conjunction with pollen therapy. Table II shows that 73.2 per cent of those patients receiving only pollen therapy obtained satisfactory relief as compared to 79.8 per cent for those who in addition received Trimeton.

SIDE REACTIONS FROM TRIMETON

Undesirable side reactions occurred in 11, or 11.7 per cent, of the 94 patients receiving Trimeton (Table III). The number of reactions was extremely low considering that the drug was taken continuously for one month. The drowsiness, dizziness, and dryness complained of was unusually mild, but occurred more frequently in the groups receiving iron in addition to the antihistaminic. In only two instances was it necessary to discontinue Trimeton because of the severity of the drowsiness.

TABLE III. SIDE REACTIONS

	TRIMETON AND IRON (34 PATIENTS)		TRIMETON (60 PATIENTS)	
COMPLAINT	NUMBER OF PATIENTS	U.S.R* (%)	NUMBER OF PATIENTS	U.S.R* (%)
Drowsiness	6	17.6	2	3.3
Dizziness	0	0	1	1.7
Drowsiness	0	0	1	1.7
Dizziness and dryness	0	0	1	1.7
Dryness and asthma	1	2.9	0	0
Asthma	1	2.9	6	10.0

*Undesirable side reactions.

Seven, or 5 per cent, of the patients experienced asthma during the hay fever season. One patient had asthma for the first time and in two others the asthma became so severe that Trimeton was discontinued with a gradual diminution of the asthmatic symptoms. These observations corroborated previous reports that the antihistaminics are of little therapeutic value in bronchial asthma and that occasionally the drugs would seem to aggravate the asthma, possibly because of a drying effect upon the respiratory membranes.[1, 8]

REACTIONS FROM POLLEN THERAPY

The 94 hay fever patients who were taking Trimeton with pollen immunization therapy did not show marked local reactions at the site of the injections. This observation verifies previous findings,[9] that antihistaminics have an inhibiting action on the production of antigen-antibody wheals. Only one patient experienced a systemic or constitutional reaction with coughing, following a single pollen injection. There was no visible local reaction.

The 56 hay fever patients receiving only pollen therapy showed the usual

moderate, and occasional marked, local reactions incident to treatment with pollen extracts. Three, or 5.3 per cent, of the patients experienced constitutional reactions, which were controlled by subcutaneous injections of epinephrine hydrochloride 1:1000.

SIDE REACTIONS FROM IRON (FERROUS SULFATE)

Complaints from the ingestion of iron were rare. The majority of the patients taking iron as ferrous sulfate, enteric-coated, tolerated the drug. Any apprehension in the patient from observing tarry stools was allayed after proper explanation. In both instances it was necessary to discontinue the iron, when one patient complained of persistent constipation and another had abdominal cramps and diarrhea.

HEMOGLOBIN STUDIES

Hemoglobin determinations performed on 164 hay fever patients prior to the onset of the ragweed hay fever season showed concentrations varying from 11.4 to 15.9 Gm. per 100 ml. of blood. These values are similar to those found in normal persons with no allergic manifestations, since hemoglobin concentrations are dependent upon various factors such as age, sex, and body variations.

One hundred and thirty of the hay fever patients were retested from 4 to 7 weeks later. Eighty-four of these had been taking 15 gr. of iron daily and 25, or 29.8 per cent, showed an increase in hemoglobin from 0.5 to 1.4 Gm. per cent. The increases have no significance in relation to the allergic conditions, since many patients showed slightly lower than normal hemoglobin concentration on the first determination, due to slight secondary anemia. Inasmuch as the group receiving iron as adjunct showed no clinical improvement over other control groups, any increase in concentration of hemoglobin after iron therapy has no significance.

To determine the effect of iron as an activator of antihistaminic agents, patients with seasonal hay fever due to ragweed who were receiving pollen therapy once weekly were given 15 gr. of ferrous sulfate in addition to 75 mg. of an antihistaminic daily for one month during the height of the ragweed pollen season. These studies were stimulated by Stavraky's observations that the action of antihistaminics such as Pyribenzamine and Antistine in relieving allergic manifestations were enhanced by the addition of iron and also relieved the lassitude and drowsiness induced by antihistaminics.

The results obtained from the addition of iron to the antihistaminic agent were not in accord with Stavraky's findings. However, it must be emphasized that all of the hay fever patients in our groups received routine immunization therapy in conjunction with an antihistaminic drug and/or iron. Stavraky, on the other hand, treated only with antihistaminic and iron. Seventy-five per cent of the fay fever patients treated with Trimeton, iron, and pollen therapy obtained satisfactory relief as compared to 81.7 per cent of the group given only Trimeton in conjunction with pollen therapy. A group of hay fever patients receiving only iron in addition to pollen therapy showed 71.5 per cent satisfactory relief as compared to 75.0 per cent of another group receiving only pollen therapy.

In comparing Stavraky's conclusions with our results, we must consider that in our investigations we employed not only complete pollen therapy but also used the more recently improved antihistaminic (Trimeton) which has shown to give comfortable symptomatic relief with minimum side effects. The effect of the addition of an adjunct (iron) would not be as noticeable as with a less satisfactory antihistaminic drug. Seventy-three and two-tenths per cent of a group of hay fever patients receiving only pollen therapy obtained satisfactory relief as compared to 79.8 per cent of another group receiving Trimeton in addition (Table II). It is important to stress at this point, that while antihistaminic drugs are helpful agents for the symptomatic relief of allergic conditions, they should not replace specific immunization procedures. Moreover, the continued use of antihistaminics has resulted in the production of asthmatic symptoms in some patients never before having had asthma, because of the possible drying effect of the drug upon the respiratory membranes. Five per cent of the hay fever patients receiving Trimeton experienced asthma and in two instances the asthma became so severe that the drug was discontinued.

SUMMARY

1. Satisfactory and comparable results were obtained from pollen therapy with Trimeton alone and with pollen therapy with Trimeton plus iron therapy.

2. These studies indicate that iron has no therapeutic value in hay fever nor does it enhance the action of antihistaminics.

We are greatly indebted to Miss Elizabeth Neuman for the hemoglobin determinations.

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DRY PATCH TESTS FOR STREPTOMYCIN SENSITIVITY*

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In an earlier paper[1] I discussed the sensitivity developed by the skin on contact with streptomycin. Prophylaxis against this condition and treatment of the rash after it developed were considered. Through experimentation the optimum strength of streptomycin to be used in patch testing was determined. It was found that concentrations of less than 1 per cent were unreliable and over 1 per cent, in a sensitive individual, could cause exacerbation of the skin eruption and constitutional symptoms of fever, chills, nausea, vomiting, headache, and malaise. It was recommended that nurses and others handling streptomycin be tested periodically (every 3 to 6 months) in order that those who had developed sensitivity, even though no rash had yet arisen, be given other types of work away from streptomycin or if this were impossible to use many precautions which were enumerated.

That this is a real problem can be attested by the number of reports in the literature of dermatitis venenata due to contact with streptomycin.[2-5] Bernard, Lotte, and Wolff[6] stated that this occurred in 1 to 3 months in 17 nurses, in 3 to 6 months in 16, and in more than 6 months in 7. Among 12 nurses who had no skin eruption although they had handled streptomycin for 9 to 12 months, 6 were positive and 6 negative on cutaneous test (strength of test solution not given). These authors felt that an eruption may not occur in subjects with positive skin reactions if the necessary precautions are taken.

With the advent of dihydrostreptomycin (hereinafter called DHS) a new problem has appeared. Will this new drug mean two separate sensitivities, are they related, or will sensitivity to one also cause sensitivity to the other? The newer preparation is supposed to be less sensitizing and to cause fewer toxic reactions.

METHOD

Testing large numbers of individuals with wet patches becomes quite time consuming and due to instability in solution, fresh streptomycin or DHS must be available, so dry patches for streptomycin and DHS were prepared somewhat after the method of Vollmer[7] for old tuberculin patches. A solution of 1 per cent streptomycin calcium chloride (or dihydrostreptomycin sulfate) was prepared in distilled water. Strips of filter paper (1 cm. in width) were dipped in the solution. These were then hung to dry in an air-circulating oven at about 40° Centigrade. The dried strips were cut into squares 1 × 1 centimeter. Two squares were applied to a strip of adhesive tape 1″ × 3″ and then pieces of crinoline were applied to the adhesive face. Each patch was then trimmed and individually packaged in a glassine envelope. The patches were not sterilized. In the case of the streptomycin patches, filter-paper squares were similarly prepared saturated with streptomycin nutrient broth. One such square was included on each adhesive strip as a control. There was no control on the dihydrostreptomycin patches.

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The patches were applied to the skin of the back over the scapula area. Before application, the skin was cleansed with acetone and allowed to dry. The patient was cautioned about keeping the patch dry and it was left in situ for 48 hours. In none of the 248 patients tested was it necessary to remove the patch sooner. The area covered by the patch was read on removal and 24 and 48 hours later.

A positive test was one which showed small, deep vesicles on an erythematous square of skin under both streptomycin or DHS areas while the control area showed only normal skin. In none of our patients was there at any time a reaction under the control area.

No gradations of the positive reaction were attempted. Some positive reactions showed more erythema than others and in some more vesicles over a greater area which had been in contact with the drug. Some positive reactions were still easily distinguishable at the end of 6 weeks after application while others had faded completely after 4 days. In every case the reaction from DHS faded sooner than that due to streptomycin.

RESULTS

In all, 248 persons were tested. There were 182 nurses of which 160 had handled streptomycin either to make solutions, give injections, or wash syringes after injection. The period these nurses had handled the drug was from 1 week to 3 years. Eight positive reactions were obtained (Table 1). Four nurses had developed the typical eruption on their hands and four had no rash. There were no nurses with finger or hand lesions who gave negative reactions. Table I gives some of the details in the case histories of these 8 and also the results of the patch tests with streptomycin and DHS. The penicillin contact test was positive in only one nurse and she was positive also to the two forms of streptomycin. Those nurses who had positive tests to streptomycin were negative to DHS unless they had handled the newer drug. All those negative to streptomycin were also negative to DHS whether they had handled the newer drug or not.

Wet patch tests were done with 5 per cent DHS on 13 nurses who had negative DHS patch reactions. Three had positive streptomycin patch tests

TABLE I. DETAILS OF EIGHT PATIENTS WHO GAVE POSITIVE SKIN REACTIONS

NO.	INITIAL	TIME HANDLED		STREPTOMYCIN PATCH			DHS PATCH			RASH PRESENT	PENICILLIN TEST (PATCH)
		MONTHS (S)	WEEKS (DHS)	48 HR.	72 HR.	96 HR.	48 HR.	72 HR.	96 HR.		
1	A.	9	0	0	+	+	0	0	0	0	0
2	N.	24	0	0	+	+	0	0	0	0	0
3	J.	12	0	0	+	+	0	0	0	0	0
4	W. A.	6	0	+	+	+	–	–	–	+	0
5	W. I.	1	2	+	+	+	0	+	+	+	+
6	M.	16	2	+	+	+	0	+	+	+	0
7	F.	24	4	0	+	+	0	+	+	0	0
8	W. E.	30	2	+	+	+	0	+	+	+	0

S = Streptomycin.
DHS = Dihydrostreptomycin.

but had not handled DHS. Six had negative streptomycin patch tests but had handled DHS. Four had negative streptomycin patch tests and had not handled DHS. All were uniformly negative.

Sixty-six patients, all with proved tuberculosis and all having been given streptomycin by injection, were tested with dry streptomycin patches. These patients had been receiving streptomycin from 10 days to 170 days—the average for all being 70 days. The time which had elapsed since the last injection was from the day tested to 395 days. The average elapsed time since the last injection was 110 days.

Of the 66 patients, 11 had been taken off streptomycin due to toxic reactions. Among these there was found one of the only 2 positive reactions in this entire group. Details of the 11 patients are given in Table II, together with the details on the other patient who had a positive reaction. The latter, although he completed the course of treatment, developed dizziness which continued as long as the drug was given.

TABLE II. DETAILS OF ELEVEN PATIENTS WHO DEVELOPED TOXIC REACTIONS DURING STREPTOMYCIN TREATMENT

NO.	INITIALS	TREATMENT PERIOD NO. OF DAYS	ELAPSED WEEKS SINCE TREATMENT	ERUPTION	DIZZINESS	VISUAL DISTURBANCES	CLEARANCE OF SYMPTOMS AFTER CESSATION	STREPTOMYCIN PATCH TESTS 48 HR.	72 HR.	96 HR.
1	J. B.	10	3	+	+	0*	+	0	0	0
2	J. T.	120	21	+	0	0	+	0	0	0
3	J. M.	42	9	0	+	+	+	+	+	+
4	W. M.	30	1½	0	+	+	+	0	0	0
5	F. C.	24	ON†	+	0	0	+	0	0	0
6	J. L.	42	30	+	0	0	+	0	0	0
7	D. H.	42	20	+	0	0	+	0	0	0
8	C. H.	54	ON‡	+	+	0	0	0	0	0
9	W. B.	120	32	+	+	+	+	0	0	0
10	B. M.	11	13§	0	+	+	+	0	0	0
11	L. H.	90	10	0	+	+	0	0	0	0
12	P. B.	120	120**	0	+	0	+	0	+	+

*Patient blind before given streptomycin. Was able to take DHS for 13 days before dizziness became severe.

†Toxic reaction on first course; none on treatment now.

‡Had eruption and dizziness on first course; now only some dizziness.

§Blurred vision and dizziness. Stopped first course; on streptomycin since with only mild dizziness.

**Course completed in spite of dizziness. May be tried on DHS.

DISCUSSION

The purpose of this paper is to present a new, simple method of testing skin sensitivity in individuals who handled streptomycin or DHS. It is believed that this has been accomplished, but in studying the results the following facts became apparent: (1) Nurses who had not come in contact with streptomycin or DHS demonstrated no contact sensitivity; (2) nurses who had handled streptomycin without becoming skin sensitive and had not handled DHS showed no contact sensitivity to DHS; (3) nurses who had handled streptomycin without becoming skin sensitive to it and had handled DHS up to one month showed no contact sensitivity to DHS; (4) nurses who had handled streptomycin and were skin sensitive to it but had not

handled DHS showed no contact sensitivity to DHS; and (5) nurses who had handled streptomycin and were skin sensitive to it and had also handled DHS were contact sensitive also to DHS.

These five factors are graphically portrayed in Table III.

TABLE III. TABULATION OF THE FIVE FACTORS ENUMERATED IN THE DISCUSSION

FACTOR	CONTACT WITH STREPTOMYCIN	SKIN SENSITIVITY TO STREPTOMYCIN	CONTACT WITH DHS	SKIN SENSITIVITY TO DHS
1	–	–	–	–
2	+	–	–	–
3	+	–	+	–
4	+	+	–	–
5	+	+	+	+

All nurses have been cautioned repeatedly on the use of rubber gloves and other prophylactic measures mentioned in the earlier paper,[1] but how well these instructions have been carried out is a matter of conjecture. One nurse, skin test positive to streptomycin continued to improve on treatment and prophylaxis even while developing skin sensitivity to DHS. Others with eruption, not under treatment, became worse while handling the new drug and developing the new sensitivity.

Eruption does not develop in every case of skin sensitivity to streptomycin or DHS but certainly those proven sensitive to either or both drugs would do better by avoidance and if this proved impossible, by rigid adherence to prophylaxis.

Apparently systemic toxic reactions to treatment with streptomycin, even though a rash is produced, do not necessarily cause the development of contact skin sensitivity to streptomycin.

SUMMARY

1. A new, simple method of testing skin sensitivity to streptomycin and DHS is described.

2. The expectancy of developing skin sensitivity to DHS in those already skin-sensitive to streptomycin is discussed.

3. The lack of relationship between injection treatment with streptomycin and the development of skin sensitivity to it is presented.

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HOW FAR CAN WIND-BORNE POLLEN BE DISSEMINATED?*

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IT was Blackley[1] who in 1868 first posed the question: "How high can pollen rise in the atmosphere, and to what distance can it travel?" Recent investigators[4, 9-12] have made use of the airplane in an attempt to determine the distribution of pollen in the upper atmosphere. With the exception of Durham,[5] such investigators used single-engine airplanes. Because of the effect of the direct blast of the propeller on slides exposed from conventional single-engine airplanes, the possibility of contamination of slides so exposed by release of particles from the surface of the plane is increased. Hence a single-engine airplane is not an ideal vehicle from which to study pollen distribution.

On a return trip from Bermuda, Durham found Alternaria spores 350 miles from the nearest land and at 8000 feet. However, he found no ragweed pollen more than 80 miles from land, although he stated that under different conditions it was easily possible that greater numbers would be found at greater distances. Although the height to which pollen is carried is of practical importance since it determines the formation of pollen clouds, the distance over which it may be carried is of even greater practical significance. The statement is sometimes made[12] that pollen can be transported hundreds of miles in the atmosphere. Much of the evidence[1, 2, 3] that can be found to support this statement is indirect, equivocal, or based on hearsay. Scandinavian investigators have been the most determined in their efforts to learn the extent of dissemination of pollen by the wind. They have presented indirect evidence based on the findings of pollen in samples of peat suggesting that tree pollen had been carried as far as 1000 kilometers (625 miles) or more (i.e., from the North American continent to Greenland). The most direct and definite data are supplied by Erdtman[6] as the result of a single transatlantic ship crossing in 1937 (May 29 to June 7). Using vacuum cleaners for catching pollen, he found pollen of trees and herbs, among other pollen, as far as 900 kilometers (560 miles) from the southern tip of Greenland.

It was because of this dearth of direct and clear-cut evidence and because of the increasing practical importance of the need for determining the distance over which pollen can be carried in the atmosphere that the author undertook a study of this problem in the ragweed season of 1947. The principle employed was to expose prepared glass slides at sea at progressively increasing distances from land and to find the last slide on which pollen was present. Slides were exposed on surface ships plying between New York and western European ports. In three instances, slides were also exposed from four-engine transport planes (C 54's) flying between New York and Bermuda.

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The course of surface ships plying between New York and most western ports of Europe is in a northeasterly direction. Because of the projection of Nantucket Island and Nova Scotia, a ship may be 345 miles out of New York and still only 142 miles from the nearest land. This has been taken into account. At the far points, critical for this study, the distance from the nearest land is shown in the tables.

PROCEDURE

Standard glass microscope slides, having one end frosted for purposes of writing and holding, were used. Slides were prepared before the onset of the ragweed season by coating them with a thin layer of petrolatum and placing them in covered slide boxes. Exposed slides were not examined until the close of the ragweed season when a portion of the slide was stained with Calberla's solution and covered with a cover slip having an area of 4.84 square centimeters. All ragweed pollen found on this area were counted.

In the case of airplanes, exposures were made by one of the pilots who placed his hand, holding a prepared slide, just outside the cockpit window. The slide was held vertically in the palm of the hand, greased surface forward, with the thumb against the frosted end. Slides were exposed at 7000 feet altitude; the time of the exposure was one minute; a new slide was exposed every 25 to 30 miles. Necessary notations were made with pencil on the frosted surface of the slide. The speed of C 54's is 200 miles an hour, an exposure of one minute representing a distance of 3⅓ miles. The course of airplanes flying between New York and Bermuda is 151°. Pilots reported that no difficulty or hardship, even at 7000 feet, was met by keeping the hand out of the cockpit window for one minute.

In the case of ships, the captain or the first mate exposed a new slide approximately every 30 miles, picking up the old one and replacing it in the covered box. Slides were exposed as high up on deck as conveniently possible and windward of the smoke stack. In most instances the vessels were cargo carrying, having a speed up to 12 to 16 knots. In several cases, in addition to exposing a slide every 30 miles, another slide was exposed for 24 hours continuously. Slides were exposed while the ships traveled eastward; once or twice they were also exposed on the return western trip. Wind directions and wind velocities were not obtained. In general, winds over the Atlantic during August and September are westerly. No exposures were made in rainy weather.

It must be emphasized that the counts made on a slide area of 4.84 sq. cm. were so made as a matter of convenience only. These counts bear absolutely no quantitative relationship to counts obtained under standard conditions of either the gravity slide method or the volumetric method. Under conditions of this study the variables were large and unknown.

Tables I, II, and III present the counts made on slides exposed from the cockpit window of commercial transport planes (C 54's). The altitude of exposure was 7000 feet which is a most severe condition under which to find pollen since it has been shown that at altitudes above 4000 feet, even over land, there is a rapid fall in the concentration of pollen and that above 6000 to 7000 feet

TABLE I

(Sept. 1, 1947. Airplane (C 54) N. Y. to Bermuda, alt. 7000 ft., Exposure 1 min.)

MILES FROM NEW YORK CITY	RAGWEED COUNT PER 4.84 SQ. CM.	DISTANCE FROM NEAREST LAND
5	2	
25	0	
50	2	
80	1	
415	1	350 miles from Virginia Capes
		353 miles from Nantucket Island
		378 miles from Delaware coast
		378 miles from Virginia mainland
		382 miles from New Jersey coast
		383 miles from Long Island

TABLE II

(Sept. 1, 1947. Airplane (C 54) N. Y. to Bermuda, alt. 7000 ft., Exposure 1 min.)

MILES FROM NEW YORK CITY	RAGWEED COUNT PER 4.84 SQ. CM.	MILES FROM NEAREST LAND
120	1	
150	1	
345	1	290*
405	1	345†

*Block Island, eastern tip of Long Island.
†Virginia Capes.

TABLE III

(Sept. 2, 1947. Airplane (C 54) N. Y. to Bermuda. Exposure 1 min.)

MILES FROM NEW YORK CITY	ALTITUDE	RAGWEED COUNT PER 4.84 SQ. CM.
5	4000 ft.	1
25	7000 ft.	0
60	7000 ft.	1
90	7000 ft.	0

there is only an occasional pollen-grain. Along with the current study in August and September 1947, slides were also exposed from the cockpit window of twin-engine airplanes (DC 3's) over areas in New York, New Jersey, Pennsylvania, Missouri, and Kentucky. The highest counts were found at 3500 feet with a dropping off above that altitude. Only in an occasional instance was a single pollen grain found at 7000 feet. In one case, a single pollen grain was also found at 9000 feet. It is, therefore, not at all surprising that the over-ocean counts are minimal.

Every precaution was taken against possible contamination of slides. The very fact that so few grains of pollen were present, speaks against the probability of contamination of slides from either the outer or the inner surfaces on the plane. The likelihood of contamination would have been entirely eliminated if exposure had been made on westerly trips, i.e., en route from Bermuda to New York or from Europe to New York, but such arrangements could not always be assured. Nevertheless, the danger of attaching significance to the finding of a single pollen grain during a given exposure is fully realized. A single grain during the very brief exposures (one minute or 3⅓ miles at 7000 feet altitude) was found in 3 instances where the distance was 290 miles or more

from the nearest land. Because of the possibility that a single grain represents contamination, the final conclusion is drawn on findings independent of those shown in Tables I and II.

In Tables I and II it is seen that the greatest distance from New York at which a ragweed pollen grain was found was 415 miles on a course of 151°. This point is 350 miles from the nearest land. Exposures shown in those tables were made on the same day on different airplanes. Not indicated in Table I are 11 additional slides exposed successively between 110 and 390 miles from New York City and exhibiting no pollen. Similarly in Table II 10 slides exhibiting no pollen at distances of 180 to 390 miles from New York are not shown.

TABLE IV

(Sept. 4 to 6, 1947. Ship N. Y. to Oslo)

MILES FROM NEW YORK CITY	RAGWEED COUNT PER 4.84 SQ. CM.	MISCELLANEOUS POLLEN PER 4.84 SQ. CM.	DISTANCE FROM NEAREST LAND
	(Sept. 4, 1947)		
0 to 24	4		
25 to 50	4	4	
	(Sept. 5, 1947)		
50 to 75	56	6	
75 to 102	22		
102 to 127	slide missing		
127 to 152	62	4	
152 to 177	12		
177 to 202	14	4	
202 to 227	2	1	
227 to 249	6	5	
249 to 275	14	5	110 miles*
275 to 300	3	1	
300 to 325	3		
	(Sept. 6, 1947)		
325 to 350	39	11	
350 to 375	6	6	112 miles†
375 to 400	0		
400 to 425	3		
425 to 450	0		
450 to 475	5		
475 to 500	0		
500 to 525	1		
525 to 550	0		100 miles†
	Continuous Exposures		
0 to 275	202	33	
275 to 525	67	12	

*Cape Cod, Mass.
†Cape Sable, Nova Scotia.

Tables IV and V give the counts made September 4 to 6, 1947, on board ships going from New York to Oslo, Norway, and to Bremen, Germany. On both trips slides were exposed for periods of 24 hours in addition to those exposed for a distance of about 25 miles. On the trip to Oslo, ragweed pollen was found in appreciable numbers on every slide up to a distance of 375 miles out of New York, and irregularly to a distance of 525 miles. Because of the considerably more northern course followed by ships going to the Scandinavian countries, it is seen in Table IV that when a ship on this course is from 275 to 525 miles out

of New York it is only 100 to 112 miles from the nearest land, either Cape Cod, Massachusetts, or Cape Sable, Nova Scotia. If the counts of the individually exposed slides in Table IV are added through the distance 275 miles, the sum of 196 is obtained for the first 24 hours. The count on the single slide exposed continuously for the same 24-hour period is 202. The two counts correspond remarkably, and in good measure excludes the likelihood that the pollen trapped on the slides was coming from sources other than the atmosphere through which the ship was passing. Similarly, the counts for the second 24-hour period (275 to 525 miles) stand 60 to 67.

TABLE V

(Ship N. Y to Bremen)

MILES FROM NEW YORK CITY	RAGWEED COUNT PER 4.84 SQ. CM.	MISCELLANEOUS POLLEN PER 4.84 SQ. CM.	DISTANCE FROM NEAREST LAND
(Sept. 4, 1947)			
19 to 32	58		
32 to 49	16		
49 to 63	7		
63 to 82	2		
82 to 100	45	2	
100 to 130	26	1	
130 to 150	86	2	
150 to 200	39	2	
(Sept. 5, 1947)			
200 to 230	1		
230 to 260	9		
260 to 270	59		
(Sept. 5 at 1600 hrs. to Sept. 6 at 1800 hrs.)			
270 to 320	79		104 miles*
Continuous Exposures			
18 to 200	144	6	
200 to 320	130		
320 to 450	0		

*Nantucket Island

On the way to Bremen, ragweed pollen was found on every slide to a distance of 320 miles from New York. The ragweed count for the single slide exposed continuously for the first 200 miles is 144 and the total for fractionally exposed slides over the same distance is 279 which, it is believed, is not beyond reasonable experimental error. The count on the slides exposed throughout the distance 200 to 320 miles is 130 and the total of the fractional counts for this distance is 148 which, again, is in striking agreement. On the course followed from New York to Bremen, a point 300 miles out of New York is 104 miles from the nearest land, Nantucket Island, off Massachusetts.

Table VI shows the counts on a trip from New York to Dublin. Pollen was found regularly up to a distance of 150 miles out of New York. On the slide exposed through the distance 300 to 540 miles out, there were three ragweed pollen grains. On the course followed from New York to Dublin, a point 300 miles out of New York is 131 miles from the nearest land, Nantucket Island. Thirteen successive slides, exposed at intervals of 30 miles at distances between

150 and 540 miles from New York, showed no pollen and are therefore not indicated in Table VI.

TABLE VI

(Ship N. Y. to Dublin)

MILES FROM NEW YORK CITY	RAGWEED COUNT PER 4.84 SQ. CM.	MISCELLANEOUS POLLEN PER 4.84 SQ. CM.	DISTANCE FROM NEAREST LAND
0 to 30	2		
30 to 60	2		
60 to 90	9		
90 to 120	0		
120 to 150	6	1	75 miles*
Continuous Exposures (Sept. 7 to 9)			
0 to 300	1		
300 to 540	3		†

*This point which is 75 miles from Nantucket Island corresponds to a distance of 135 miles from New York.

†A point on this ship's course 300 miles from New York corresponds to a distance of 131 from Nantucket Island, off Massachusetts.

Table VII, presenting the counts on the trip between New York and Antwerp, shows that ragweed pollen was found as far out as 330 to 360 miles from New York. On this course a point 345 miles out of New York is 142 miles from the nearest land, Nantucket Island.

TABLE VII

(Ship N. Y. to Antwerp)

MILES FROM NEW YORK CITY	RAGWEED COUNT PER 4.84 SQ. CM.	MISCELLANEOUS POLLEN PER 4.84 SQ. CM.	DISTANCE FROM NEAREST LAND
(Sept. 6, 1947)			
0 to 30	6		
30 to 60	1	1	
60 to 90	0		
90 to 120	0		
(Sept. 7, 1947)			
120 to 150	0		
150 to 180	1	1	
180 to 210	2	1	
210 to 240	2		
240 to 270	11		
270 to 300	5		
300 to 330	3		
330 to 360	3		142 miles*
360 to 390	0		
390 to 420	0		
Continuous Exposure			
0 to 270	28	4	

*From Nantucket Island. This mileage corresponds to a distance averaging 330 and 360 miles (i.e., 345 miles from New York).

Table VIII presents the results of exposure of slides on a vessel going from New York to Southampton. Exposures were begun when the ship was 300 miles out of New York and were continued up to a distance of 1090 miles out. Ragweed pollen was present on each of the first 6 successive slides to a distance of 520 miles. Once again it may be pointed out that the failure to find a single

ragweed grain on any of the next 18 slides is evidence against the probability that contamination had taken place on the ragweed pollen-containing slides. The nearest land at a point 500 miles out of New York on the course taken to Southampton is 201 miles away (Cape Sable, Nova Scotia).

TABLE VIII

(Ship N. Y. to Southampton)

MILES FROM NEW YORK CITY	RAGWEED COUNT PER 4.84 SQ. CM.	MISCELLANEOUS POLLEN PER 4.84 SQ. CM.	MILES FROM NEAREST LAND*
(Sept. 6, 1947)			
300 to 340	8		154‡
340 to 370	1		175†
370 to 410	1	1	173†
(Sept. 7, 1947)			
410 to 440	64	2	174†
440 to 480	2	1	180†
480 to 520	2		201†

*As measured from a point averaging the two distances indicated in the first column.
†From Cape Sable, Nova Scotia.
‡From Nantucket Island, off Massachusetts.

Exposures were made on 10 other vessels, but since they were made either at the very beginning of the ragweed season (for example, August 16, 1947, to Oslo and Copenhagen, one ragweed grain 50 to 75 miles out of New York), or at the end of the season (for example, September 29, 1947, on a return trip from Lisbon, to Norfolk, Va., 21 ragweed grains 50 to 25 miles away from Norfolk) the counts were minimal or zero and are not presented in detail. The negative counts in these instances are in themselves significant.

In interpreting the findings in this study, a conservative position is taken. In each case the nearest point of land is taken as the probable source of the pollen encountered, although such near point may not be supporting a luxurious growth of ragweed. For example, although no pollen counts are available for Nova Scotia, it is known that that land mass is not heavily infested with ragweed. Furthermore, by references to surface weather maps and recorded observations of wind movements aloft, the trajectory of an air mass present at a given time and place can be determined and the origin of this air mass identified. Thus, it is almost certain that the mass of air 200 miles south of Cape Sable, Nova Scotia, at approximately 8 A.M. on Sept. 7, 1947, (Table VIII) originated from the Massachusetts-Rhode Island area. This means that the pollen in this air in all likelihood traveled 300 to 350 miles instead of the 201 miles indicated in the table which is the distance from the nearest point of land.

One of the practical considerations which led to this study was the current attempts in one large metropolitan area to free ragweed hay fever sufferers of their symptoms by eradicating the ragweed plant from within its boundaries. If the findings in the present study are correct, it is clear that it will be most difficult to attain such a planned goal in a community not protected by mountains or by wide stretches of water.

SUMMARY

1. On the basis of ragweed pollen found on slides exposed on 15 ships traveling between New York City and European ports in 1947, it is believed that ragweed pollen can be transported in the atmosphere, under suitable conditions of weather, a distance of at least 200 miles.

2. These findings on board ship are supported by the suggestive findings on slides exposed from multi-engine airplanes flying between New York City and Bermuda.

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Editorial

Twenty Years

IN NOVEMBER, 1929, the date which marked the onset of the great financial depression, the first issue of the JOURNAL OF ALLERGY appeared. There was a proper place for such a periodical, for interest in allergy was high, although scattered. Annual meetings of the two national societies were the only focal points of presentation of work done, but the proceedings were not published. Thus, with a wealth of good material and high promise, the new JOURNAL was launched.

As the financial depression deepened, fewer manuscripts were submitted to medical periodicals. Our backlog gradually became used up and subscriptions fell off to a point of discouragement both for the editor and the publisher. As submitted material diminished it became necessary for the editorial board to be less discriminating and this was reflected in the quality of the JOURNAL. However, the JOURNAL OF ALLERGY has always had an editorial policy wherein emphasis has been placed on investigation, be it clinical or pure research, for this expressed progress. There was sufficient singleness of this purpose to attract current research, and as this slowly improved, so did the JOURNAL. Today, it is in the comfortable position of having a healthy backlog of selected material, a substantial subscription list, and, above all, the respect of good medical opinion.

A new era in allergy is coming into being, due to the "rediscovery" that human hypersensitiveness may be responsible for the symptoms of rheumatic fever, acute nephritis, arteritis, and a variety of other clinical disorders. This has attracted widespread interest which is growing. Allergy as applied to such situations has the same validity as it has in hay fever, for the lesions of each are mediated by immune mechanisms.

To this important aspect of clinical allergy, the allergist has contributed comparatively little and leadership is in other hands. The JOURNAL cannot hope to capture much of this material until members of the Academy participate sufficiently in this newer field, for manuscripts read at the annual meetings utilize much of its space. However, the Editorial Board is committed to seek manuscripts on all phases of allergy, be they clinical or experimental in content, provided only they are of high standard. It is hoped thereby that the JOURNAL will catch up and then keep abreast of current thought. Otherwise its effectiveness will diminish, and it will lose its place in the ranks of good medical periodicals. Should it succeed, it will represent allergy on a higher level and during the next twenty years its pages should record much that is fundamental, as knowledge of human hypersensitiveness unfolds.

H. L. A.

Book Reviews

PROGRESS IN ALLERGY, edited by Paul Kallós, Basel and New York, 1949, S. Karger, pp. 352.

The first edition of this collection of treatises by various contributors appeared some ten years ago and it is timely that progress in allergy during the intervening period be recorded. This has been but partly achieved and much is missing. The fault seems to lie first in the way the book is assembled in that there is no uniform plan of presentation by the several contributors. Consequently, there are chapters such as "Immunochemistry," by Kabat, which although not oriented to allergy describe the great advances during the decade; a fine presentation of "Allergy in Diseases of the Skin," by Haxthausen of Copenhagen, which, although not always in conformity with the American point of view, is on a high level. "The Pharmacology of Antihistaminics," by R. Meier and K. Bucker of Basel, is also an excellent critical review (although written in German). Another impressive chapter is "Allergy of the Middle Ear," by Koch of Stockholm. This is a scholarly piece of work documented by both clinical and animal research. On the other hand, such contributions as "An Etiological Survey of Chronic Urticaria," by Waldbott, based essentially on personal observations in 158 cases, "Small Dosage Dust and Pollen Therapy," by Hansel, advocating a personal adaptation wherein optimum dosage varies from 1:10 billion to 1:100,000, a chatty chapter on "Allergy of the Nervous System with Special Reference to Migraine" with no references, by Foster Kennedy, containing little that was not said at the time of the first edition, make the quality of the book very uneven. "Allergic Diseases in Animals," by Wittich, "Present Status of Aerosol Therapy of the Lungs and Bronchi," by Abramson, and "Allergy to Human Dander in Infantile Eczema," by Simon, are well done.

Another obvious criticism concerns the complete omission of so much of progress in allergy during the past decade. Although in the preface, the editor states, "These volumes are to reflect the development in the whole field of allergy," such significant contributions as those of Rich and Gregory, Ehrlich and his associates, Raffel, Hawn and Janeway, Dammin and Bukantz, the Caveltis, Reube, and many others are not even mentioned and thus the book fails its purpose.

POLLEN SLIDE STUDIES, by Grafton Tyler Brown, M.D., Springfield, Ill., 1949, Charles C Thomas, Publisher, pp. 122, illustrated.

The preparation of the slides and the method of counting atmospheric pollen and the influence of meteorologic conditions upon pollination are briefly presented in separate short chapters. There is also the complete pollen, mold, and smut spore count in Washington, D. C., for the years 1938 and 1941.

The greater part of the book is made up of brief descriptions accompanied by detailed sketches of the oil immersion magnification from specimen slides, diagrammatic sketches, and photomicrographs of the various pollen, mold, and smut spores identified on the slides, exposed in Washington, D. C., by the author.

There is no correlation of these atmospheric entities with clinical problems. Grass pollen are not differentiated, all being lumped under the term Poaceae or Gramineae.

In essence, this is a pictorial review of the author's experience with pollen slides and will serve as an elementary guide for those who attempt the identification of mold and smut spores, and of pollen in the dry or unexpanded state.

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